

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



AUZ

(11)

EP 1 256 574 A1

(12)

EUROPEAN PATENT APPLICATION
published in accordance with Art. 158(3) EPC

(43) Date of publication:

13.11.2002 Bulletin 2002/46

(51) Int Cl.⁷: **C07D 209/48**

(21) Application number: 01902730.9

(86) International application number:
PCT/JP01/00721

(22) Date of filing: **01.02.2001**

(87) International publication number:
WO 01/056988 (09.08.2001 Gazette 2001/32)

(84) Designated Contracting States:

AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR

- IIJIMA, Hiroshi
Takasaki-shi, Gunma 370-1295 (JP)
- IWAKUBO, Masayuki
Takasaki-shi, Gunma 370-1295 (JP)
- OKADA, Yuji
Takasaki-shi, Gunma 370-1295 (JP)

Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 01.02.2000 JP 2000024292

(74) Representative: **HOFFMANN EITLE**
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München (DE)

(71) Applicant: KIRIN BEER KABUSHIKI KAISHA

Tokyo 104-8288 (JP)

(72) Inventors:

- TAKAMI, Atsuya
Takasaki-shi, Gunma 370-1295 (JP)

(54) NITROGEN-CONTAINING COMPOUNDS HAVING KINASE INHIBITORY ACTIVITY AND DRUGS CONTAINING THE SAME

(57) An objective of the present invention is to provide compounds having Rho kinase inhibitory activity. The compounds according to the present invention are those represented by formula (I) or pharmaceutically acceptable salts or solvates thereof:

example, pyridyl or phthalimide; X represents group (i) -NH-C(=O)-NH-Q1-, group (ii) -NH-C(=O)-Q2-, wherein Q1 and Q2 represent a bond, alkylene, or alkenylene, or the like; and Z represents hydrogen, halogen, a monocyclic, bicyclic, or tricyclic carbocyclic group, a heterocyclic group or the like, for example, optionally substituted phenyl.

Het-X-Z

(I)

wherein Het represents a monocyclic or bicyclic heterocyclic group containing at least one nitrogen atom, for

Description**BACKGROUND OF THE INVENTION**5 **Field of the Invention**

[0001] The present invention relates to compounds having Rho kinase inhibitory activity and more particularly to compounds usable for the therapy of diseases mediated by Rho kinase.

10 **Related Art**

[0002] It has been clarified that Rho is activated upon the receipt of signals from various cell membrane receptors, and the activated Rho functions, through ROCK/Rho kinase and, further, actomyosin system, as a molecular switch of a wide variety of cellular phenomena such as smooth muscle contraction, cell movement, cell adhesion, change in character of cells (formation of actin stressed fibers), control of cell division (sthenia of cytokinesis or activation of gene transcription), platelet aggregation, leukocyte aggregation, cell proliferation, sthenia of carcinogenesis and invasion of cancer and the like.

[0003] The contraction of smooth muscle is deeply involved in the pathology of hypertension, angina pectoris, vasospasm, for example, cardiovascular contraction and cerebrovascular contraction, asthma, peripheral circulatory disorder, threatened premature birth, glaucoma, constriction of visual field, pollakiuria, impotence and the like. Cell movement plays an important role in invasion/metastasis of cancer, arteriosclerosis, retinopathy, immune response and the like. Cell adhesion is deeply involved in metastasis of cancer, inflammation, and autoimmune diseases. The alteration of morphology of cells is deeply involved in cerebral dysfunction, osteoporosis, microbism and the like. Cell proliferation is deeply involved in cancer, arteriosclerosis and the like. Thus, Rho is deeply involved in various diseases.

[0004] ROCK or ROCK I (Japanese Patent Laid-Open No. 135683/1997; and T. Ishizaki et al., EMBO J., Vol. 15, No. 8, pp 1885-1893 (1996)) and Rho kinase or ROCK II (Japanese Patent Laid-Open No. 113187/1998; and T. Matsui et al., EMBO J., Vol. 15, No. 9, pp 2208-2216 (1996)) are reported as serine/threonine kinase which is activated upon the activation of Rho. They have been proven to be isozymes (O. Nakagawa et al., FEBS Lett., Vol. 392, No. 2, pp 189-193 (1996)).

[0005] Compounds having ROCK/Rho kinase inhibitory activity include trans-4-amino(alkyl)-1-pyridylcarbamoylcyclohexane compounds (WO 90/05723), benzamide compounds (WO 95/28387), Y-27632 (Uehata, M., Ishizaki, T. et al.: Nature, 389: 990-994, 1997), and fasudil hydrochloride commercially available as cerebrovascular contraction inhibitor (HA-1077, Asahi Kasei kogyo K.K.) (Ono-Saito, N., Niki, I., Hidaka, H. : Pharmacol. Ther., 123-131, 1999). Further, WO 98/06433 discloses ROCK/Rho kinase inhibitors.

35 **SUMMARY OF THE INVENTION**

[0006] The present inventors have found that certain nitrogen-containing compounds have Rho kinase inhibitory activity (Pharmacological Test Example 1).

[0007] The present inventors have further found that certain nitrogen-containing compounds have leukocyte migration inhibitory activity (Pharmacological Test Example 2).

[0008] The present inventors have further found that certain nitrogen-containing compounds have albuminuria amelioration activity in anti-GBM model rats (Pharmacological Test Examples 3 and 4).

[0009] The present inventors have further found that certain nitrogen-containing compounds have blood antihypertensive activity in spontaneously hypertensive rats (Pharmacological Test Example 5).

[0010] An object of the present invention is to provide compounds having Rho kinase inhibitory activity.

[0011] Another object of the present invention is to provide a pharmaceutical composition for use in the treatment of diseases mediated by Rho kinase.

[0012] According to the present invention, there is provided a compound represented by formula (I) or a pharmaceutically acceptable salt or solvate thereof:

Het-X-Z

(I)

55 wherein

Het represents a five- to seven-membered monocyclic saturated or unsaturated heterocyclic group containing at least one nitrogen atom, or a nine- to twelve-membered bicyclic saturated or unsaturated heterocyclic group containing at least one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by a halogen

atom, an oxygen atom, hydroxyl, or C₁₋₄ alkylcarbonyl,

X represents a group selected from the group consisting of groups (i) to (ix):

5

(i) -NH-C(=O)-NH-Q1-

wherein

Q1 represents

a bond,

alkylene having 1 to 4 carbon atoms, or

10 alkenylene having 2 to 4 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alcoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is 15 optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

15

(ii) -NH-C(=O)-Q2-

20

wherein

Q2 represents

a bond,

alkylene having 1 to 5 carbon atoms, or

25 alkenylene having 2 to 5 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alcoxycarbonyl of which the alkyl portion is 30 optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

30

(iii) -NH-C(=O)-Q3-Q4-Q5-

35 wherein

Q3 represents

alkylene having 1 to 4 carbon atoms or

alkenylene having 2 to 4 carbon atoms,

40 Q4 represents -O-, -NH-, or -S(=O)m- wherein m is an integer of 0 to 2,

Q5 represents

a bond,

alkylene having 1 to 3 carbon atoms, or

45 alkenylene having 2 or 3 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alcoxycarbonyl of which the alkyl portion is 50 optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

50

(iv) -N(-R¹)-Q6-Q7-

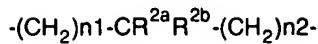
wherein

R¹ represents a hydrogen atom or C₁₋₄ alkylcarbonyl,

55 Q6 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

Q7 represents

a bond,



wherein

- 5 n1 and n2 are each an integer of 0 to 3,
when n2 is 2 or 3, $-\text{CH}_2\text{-CH}_2\text{-}$ in $-(\text{CH}_2)n2\text{-}$ may represent $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$,
 R^{2a} and R^{2b} , which may be the same or different, represent
a hydrogen atom,
a halogen atom,
- 10 C_{1-6} alkyl optionally substituted by hydroxyl, carboxyl,
 C_{1-4} alkoxy carbonyl,
cyano,
 $-(\text{C}=\text{O})\text{-N}(-\text{R}^{2c})(-\text{R}^{2d})$ wherein R^{2c} and R^{2d} , which may be the same or different, represent a hydrogen atom; C_{1-4} alkyl optionally substituted by a halogen atom; C_{1-4} alkoxy optionally substituted by a halogen atom; cyclopropyl; or
15 benzyl of which the phenyl portion is optionally substituted by one or two C_{1-4} alkoxy's, or
phenyl optionally substituted by a halogen atom; hydroxyl; nitro; amino; C_{1-4} alkyl optionally substituted by a halogen atom; C_{1-4} alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,
- 20 $-(\text{CH}_2)\text{p-NR}^3\text{-}$ wherein p is an integer of 0 to 2, R^3 represents a hydrogen atom, C_{1-4} alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C_{1-4} alkyl optionally substituted by a halogen atom; C_{1-4} alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or
25 benzyloxy,
 $-\text{NH}-(\text{CH}_2)\text{q1-CR}^{4a}\text{R}^{4b}-(\text{CH}_2)\text{q2-}$ wherein q1 and q2 are each an integer of 0 to 2 and R^{4a} and R^{4b} each independently represent a hydrogen atom, C_{1-4} alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C_{1-4} alkyl optionally substituted by a halogen atom; C_{1-4} alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,
- 30 $-(\text{C}=\text{O})\text{-O-CR}^{4a}\text{R}^{4b}\text{-CH}_2\text{-}$ wherein R^{4a} and R^{4b} are as defined above,
 $-\text{NH}-(\text{CH}_2)\text{i-NH-}$ wherein i is an integer of 1 to 4, or
35 $-\text{S}(=\text{O})\text{j-}$ wherein j is 0, 1, or 2,

(v) -NH-Q8-Q9-Q10-

40 wherein

Q8 represents

alkylene having 1 to 5 carbon atoms or
alkenylene having 2 to 5 carbon atoms,

Q9 represents $-\text{O}-$, $-\text{NH}-$, or $-\text{S}(=\text{O})\text{r-}$ wherein r is an integer of 0 to 2,

45 Q10 represents

a bond,

alkylene having 1 to 3 carbon atoms, or

50 alkenylene having 2 or 3 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C_{1-4} alkyl or phenyl optionally substituted by a halogen atom; hydroxyl; nitro; amino; C_{1-4} alkyl optionally substituted by a halogen atom; C_{1-4} alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C_{1-4} alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

55

(vi)-O-Q11-Q12-

wherein

Q11 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

Q12 represents
a bond,

5 -(CH₂)_s-CHR⁵- wherein s is an integer of 0 to 2 and R⁵ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

10 -(CH₂)_t-NR⁶- wherein t is an integer of 0 to 2 and R⁶ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy, or

15 -NH-(CH₂)_u-CHR⁷- wherein u is an integer of 0 or 1 and R⁷ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

25 (vii)-Q13-Q14-

wherein

Q13 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

30 Q14 represents
a bond,

-(CH₂)_v-CHR⁸- wherein v represents an integer of 0 to 2 and R⁸ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

35 -(CH₂)_w-NR⁹- wherein w represents an integer of 0 to 2 and R⁹ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

40 -NH-(CH₂)_x-CHR¹⁰- wherein x is an integer of 0 or 1 and R¹⁰ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

45 (viii) -C(=O)-Q15-(CH₂)_y-

50 wherein Q15 represents a five- to seven-membered saturated or unsaturated heterocyclic group and this heterocyclic group is optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl and y is an integer of 0 to 4, and

(ix) -C(=O)-NR¹-Q16-(CH₂)_z-

wherein R¹ is as defined above, Q16 represents a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl, and z represents an integer of 0 to 4,

Z represents

a hydrogen atom,
a halogen atom,

a three- to seven-membered saturated or unsaturated monocyclic carbocyclic or heterocyclic group,

a nine- to twelve-membered bicyclic saturated or unsaturated carbocyclic or heterocyclic group, or

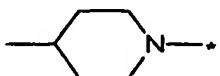
a thirteen- to fifteen-membered tricyclic saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic and heterocyclic groups are optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy of which the phenyl portion is optionally substituted by a halogen atom,

provided that

when X represents group (i) wherein Q1 represents a bond and Z represents 2-ethoxycarbonyl-phenyl, 2-methoxy-phenyl, 2-nitro-phenyl, or 4-nitro-phenyl, Het does not represent 4-pyridyl, and

when X represents group (iv) wherein R¹ represents a hydrogen atom, Q6 represents formula

20



25 wherein the bond with * represents a bond to Q7, and Q7 represents -CH₂-CH₂-, and Z represents an unsubstituted phenyl, Het does not represent 1-piperidinyl, 4-morpholinyl, 3-pyridinyl, 4-pyridinyl, 2-chloro-3-pyridinyl, 2-chloro-5-pyridinyl, 5-indolyl, 5-indazolyl, 3-quinolinyl, or 2,1,3-benzothiadiazol-4-yl.

30 [0013] The compounds according to the present invention are useful for the treatment of diseases mediated by Rho kinase.

[0014] According to the present invention, there is provided a pharmaceutical composition comprising a compound represented by formula (Ia) or a pharmaceutically acceptable salt or solvate thereof, for use in the therapy of diseases mediated by Rho kinase:

35 Het-X-Z (Ia)

wherein

40 Het represents a five- to seven-membered monocyclic saturated or unsaturated heterocyclic group containing at least one nitrogen atom, or a nine- to twelve-membered bicyclic saturated or unsaturated heterocyclic group containing at least one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by a halogen atom, an oxygen atom, hydroxyl, or C₁₋₄ alkyl carbonyl,

X represents a group selected from the group consisting of groups (i) to (ix):

45 (i) -NH-C(=O)-NH-Q1-

wherein

Q1 represents

a bond,

alkylene having 1 to 4 carbon atoms, or

50 alkenylene having 2 to 4 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

(ii) -NH-C(=O)-Q2-

wherein

- 5 Q2 represents
a bond,
alkylene having 1 to 5 carbon atoms, or
alkenylene having 2 to 5 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄
10 alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted
by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl
15 of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is
optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by
a halogen atom; or benzyloxy,

15 (iii) -NH-C(=O)-Q3-Q4-Q5-

wherein

- 20 Q3 represents
alkylene having 1 to 4 carbon atoms or
alkenylene having 2 to 4 carbon atoms,
Q4 represents -O-, -NH-, or -S(=O)m- wherein m is an integer of 0 to 2,
Q5 represents
a bond,
25 alkylene having 1 to 3 carbon atoms, or
alkenylene having 2 or 3 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄
alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted
30 by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl
of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is
optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by
a halogen atom; or benzyloxy,

(iv) -N(-R¹)-Q6-Q7-

35 wherein

- R¹ represents a hydrogen atom or C₁₋₄ alkyl carbonyl,
Q6 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group
40 and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,
Q7 represents
a bond,

45 -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2-

wherein

- n1 and n2 are each an integer of 0 to 3,
when n2 is 2 or 3, -CH₂-CH₂- in -(CH₂)n2- may represent -CH=CH- or -C≡C-,
R^{2a} and R^{2b}, which may be the same or different, represent
50 a hydrogen atom,
a halogen atom,
C₁₋₆ alkyl optionally substituted by hydroxyl, carboxyl,
C₁₋₄ alkoxy carbonyl,
cyano,
55 -(C=O)-N(-R^{2c})(-R^{2d}) wherein R^{2c} and R^{2d}, which may be the same or different, represent a hydrogen atom; C₁₋₄
alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy optionally substituted by a halogen atom; cyclopropyl; or
benzyl of which the phenyl portion is optionally substituted by one or two C₁₋₄ alkoxy's, or
phenyl optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a

halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

5 -(CH₂)^p-NR³- wherein p is an integer of 0 to 2, R³ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or
10 benzyloxy,

15 -NH-(CH₂)^{q1}-CR^{4a}R^{4b}-(CH₂)^{q2}- wherein q1 and q2 are each an integer of 0 to 2 and R^{4a} and R^{4b} each independently represent a hydrogen atom, C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

20 -(C=O)-O-CR^{4a}R^{4b}-CH₂- wherein R^{4a} and R^{4b} are as defined above,

-NH-(CH₂)ⁱ-NH- wherein i is an integer of 1 to 4, or

-S(=O)^j- wherein j is 0, 1, or 2,

(v) -NH-Q8-Q9-Q10-

wherein

25 Q8 represents

alkylene having 1 to 5 carbon atoms or
alkenylene having 2 to 5 carbon atoms,

Q9 represents -O-, -NH-, or -S(=O)r- wherein r is an integer of 0 to 2,

Q10 represents

30 a bond,

alkylene having 1 to 3 carbon atoms, or

35 alkenylene having 2 or 3 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or phenyl optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

40 (vi)-O-Q11-Q12-

wherein

45 Q11 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

Q12 represents

a bond,

50 -(CH₂)^s-CHR⁵- wherein s is an integer of 0 to 2 and R⁵ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

55 -(CH₂)^t-NR⁶- wherein t is an integer of 0 to 2 and R⁶ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy, or

5 -NH-(CH₂)_u-CHR⁷- wherein u is an integer of 0 or 1 and R⁷ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

10 (vii)-Q13-Q14-

15 wherein

Q13 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

20 Q14 represents

a bond,

25 -(CH₂)_v-CHR⁸- wherein v represents an integer of 0 to 2 and R⁸ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

30 -(CH₂)_w-NR⁹- wherein w represents an integer of 0 to 2 and R⁹ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy, or

35 -NH-(CH₂)_x-CHR¹⁰. wherein x is an integer of 0 or 1 and R¹⁰ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

40 (viii) -C(=O)-Q15-(CH₂)_y-

wherein Q15 represents a five- to seven-membered saturated or unsaturated heterocyclic group and this heterocyclic group is optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl and y is an integer of 0 to 4, and

45 wherein R¹ is as defined above, Q16 represents a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl, and z represents an integer of 0 to 4,

50 Z represents

a hydrogen atom,

a halogen atom,

55 a three- to seven-membered saturated or unsaturated monocyclic carbocyclic or heterocyclic group, a nine- to twelve-membered bicyclic saturated or unsaturated carbocyclic or heterocyclic group, or a thirteen- to fifteen-membered tricyclic saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic and heterocyclic groups are optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy of which the phenyl portion is optionally substituted by a halogen atom.

(ix) -C(=O)-NR¹-Q16-(CH₂)_z-

DETAILED DESCRIPTION OF THE INVENTION

Compound

- 5 [0015] The terms "alkyl," "alkoxy," "alkenyl," "alkylene," and "alkenylene" as used herein as a group or a part of a group respectively mean straight chain or branched chain alkyl, alkoxy, alkenyl, alkylene, and alkenylene.
- [0016] Examples of C₁₋₄ alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, i-butyl, s-butyl, and t-butyl.
- [0017] Examples of C₁₋₄ alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, and t-butoxy.
- 10 [0018] The expression "alkyl optionally substituted by" as used herein means alkyl, on which one or more hydrogen atoms are optionally substituted by one or more substituents which may be the same or different. It will be apparent to a person skilled in the art that the maximum number of the substituents can be determined depending upon the number of substitutable hydrogen atoms on the alkyl group. This can apply to groups having substituents other than alkyl.
- 15 [0019] The term "halogen atom" as used herein means a fluorine, chlorine, bromine, or iodine atom.
- [0020] Examples of the saturated or unsaturated monocyclic three- to seven-membered carbocyclic group include cyclopropyl, cyclopentyl, cyclohexyl, and phenyl.
- [0021] The saturated or unsaturated monocyclic five- to seven-membered heterocyclic ring may contain one or more hetero-atoms selected from oxygen, nitrogen, and sulfur atoms.
- 20 [0022] Examples of the saturated or unsaturated monocyclic five- to seven-membered heterocyclic group include pyridyl, furanyl, piperidyl, pyrimidyl, imidazolyl, thienyl, thiophenyl, isoxazoyl, isothiazoyl, 1,2,3-oxadiazoyl, furazanyl, 1,2,3-triazoyl, 1,2,4-triazoyl, pyridazyl, pyrrolinyl, pyronyl, morphonyl, and triazinyl.
- [0023] Examples of the saturated or unsaturated bicyclic nine- to twelve-membered carbocyclic group include naphthalenyl, naphthyl, and indenyl.
- 25 [0024] Examples of saturated or unsaturated bicyclic nine- to twelve-membered, preferably nine- or ten-membered, heterocyclic group include indolyl, quinolinyl, quinazolinyl, 1,3-benzodioxole, isoindolyl, indazolyl, 1H-pyrazolo[3,4-d]pyrimidyl, benzotriazolyl, isoquinolinyl, sinolinyl, phthalazinyl, pteredinyl, naphthyridinyl, benzimidazolinyl, benzothiazolinyl, benzoxazolinyl, 3,4-methylenedioxyphenyl, and benzo[6]furanyl.
- [0025] Examples of the saturated or unsaturated tricyclic thirteen- to fifteen-membered carbocyclic or heterocyclic group include fluorenyl, carbazolyl, phenothiazinyl, and phenoxazinyl.
- 30 [0026] In formulae (I) and (Ia), Het may be a five- to seven-membered monocyclic saturated or unsaturated heterocyclic group containing at least one, preferably 1 to 3, nitrogen atoms, preferably a heterocyclic group containing only a nitrogen atom as the hetero-atom.
- [0027] In formulae (I) and (Ia), the monocyclic heterocyclic group represented by Het preferably represents formula (IIa), (IIb), or (IIc):



40 wherein A1 represents a five- to seven-membered monocyclic saturated or unsaturated heterocyclic group having at least one nitrogen atom.

- 45 [0028] In formulae (I) and (Ia), more preferably, the monocyclic heterocyclic group represented by Het represents 1,2,3-triazoyl, 1,2,4-triazoyl, and pyrrolinyl represented by formula (IIa), pyridyl, pyrimidyl, isoxazoyl, isothiazoyl, furazanyl, and triazinyl represented by formula (IIb), and 1,2,3-oxadiazoyl and pyridazyl represented by formula (IIc).
- [0029] In formulae (I) and (Ia), Het may represent a nine- to twelve-membered bicyclic saturated or unsaturated heterocyclic group containing at least one, preferably 1 to 3, nitrogen atoms, preferably a heterocyclic group containing only a nitrogen atom as the hetero-atom.
- 50 [0030] In formulae (I) and (Ia), the bicyclic heterocyclic group represented by Het preferably represents formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj):

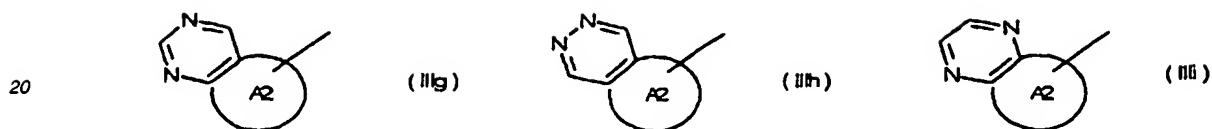
5



10



15



25

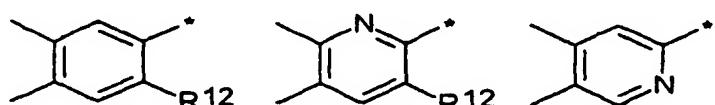


30

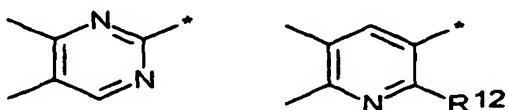
wherein A2 represents phenyl optionally substituted by a halogen atom, or an unsaturated six-membered heterocyclic ring which is optionally substituted by a halogen atom and contains one or two nitrogen atoms; R11 represents a hydrogen atom or C₁₋₄ alkylcarbonyl; and E represents -NH-, -O-, or -S-.

[0031] Preferably, the A2 portion represents a group selected from the group consisting of the following groups:

40



45



50

wherein R12 represents a hydrogen atom or a halogen atom; and a bond with * represents a bond to group X with the remaining two bonds each representing a bond to the heterocyclic group.

[0032] In formulae (I) and (Ia), more preferred examples of the bicyclic heterocyclic group represented by Het include:

55

1H-5-indazolyl, 1-acetyl-1H-5-indazolyl and 1H-pyrazolo[3,4-d]pyrimidin-4-yl represented by formula (IIIa); 1H-5-benzotriazolyl represented by formula (IIIb); 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl and 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl represented by formula (IIIc);

isoquinolinyl represented by formula (IIId);
 sinolinyl represented by formula (IIIe);
 quinolinyl and naphthyridinyl represented by formula (IIIf);
 5 quinazolinyl represented by formula (IIIg);
 phthalazinyl represented by formula (IIIh);
 pteridinyl represented by formula (IIIi); and
 benzimidazolinyl, benzothiazolinyl and benzoxazolinyl represented by formula (IIIj).

[0033] In formulae (I) and (Ia), an example of preferred group (i) represented by X is that Q1 represents a bond, alkylene having 1 to 3 carbon atoms, or alkenylene having 2 or 3 carbon atoms and the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl.

[0034] In formulae (I) and (Ia), an example of preferred group (ii) represented by X is that Q2 represents a bond, alkylene having 1 to 3 carbon atoms, or alkenylene having 2 or 3 carbon atoms and the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl.

[0035] In formulae (I) and (Ia), an example of preferred group (iii) represented by X is that Q3 represents alkylene having 1 or 2 carbon atoms or alkenylene having 2 carbon atoms; Q4 represents -O-, -NH-, or -S(=O)m- wherein m is an integer of 0 to 2; and Q5 represents a bond, alkylene having 1 or 2 carbon atoms, or alkenylene having 2 carbon atoms and the alkylene and alkenylene represented by Q5 represent C₁₋₄ alkyl or optionally substituted phenyl.

[0036] In formulae (I) and (Ia), an example of preferred group (iv) represented by X is that R¹ represents a hydrogen atom or C₁₋₄ alkylcarbonyl; Q6 represents a bond, a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents a bond, -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2-, wherein n1 is an integer of 0 or 1, n2 is 0, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, -(CH₂)p-NR³-, wherein p is an integer of 0 or 1 and R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, or -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2- wherein q1 is 0 or 1, q2 is 0, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl or optionally substituted phenyl.

[0037] Another example of preferred group (iv) represented by X is that R¹ represents a hydrogen atom or C₁₋₄ alkylcarbonyl; Q6 represents a bond, a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents a bond, -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2-, wherein n1 and n2 are each an integer of 0 to 3, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, optionally substituted C₁₋₆ alkyl, carboxyl, C₁₋₄ alkoxy carbonyl, cyano, -(C=O)-N(-R^{2c})(-R^{2d}), wherein R^{2c} and R^{2d}, which may be the same or different, represent a hydrogen atom, optionally substituted C₁₋₄ alkyl, optionally substituted C₁₋₄ alkoxy, cyclopropyl, or optionally substituted benzyl, or optionally substituted phenyl, -(CH₂)p-NR³-, wherein p is an integer of 0 or 1, R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2-, wherein q1 and q2 are each an integer of 0 to 2, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, -(C=O)-O-CR^{4a}R^{4b}-CH₂, wherein R^{4a} represents a hydrogen atom and R^{4b} represents a hydrogen atom, optionally substituted C₁₋₆ alkyl, or optionally substituted phenyl, -NH-(CH₂)i-NH-, wherein i is an integer of 1 to 4, or -S(=O)- wherein j is 0, 1, or 2.

[0038] In formulae (I) and (Ia), an example of more preferred group (iv) represented by X is that R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom; and Q7 represents -(CH₂)p-NR³-, wherein p is an integer of 0 or 1 and R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, or -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2-, wherein q1 is 0 or 1, q2 is 0, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.

[0039] Another example of more preferred group (iv) represented by X is that R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated heterocyclic group which is optionally substituted by an oxygen atom and contains one nitrogen atom; and Q7 represents -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 is an integer of 0 or 1, n2 is 0, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.

[0040] Still another example of more preferred group (iv) represented by X is that R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 and n2, which may be the same or different, are each an integer of 0 to 3, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom or optionally substituted C₁₋₄ alkyl.

[0041] A further example of more preferred group (iv) represented by X is that R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen

atom; and Q7 represents $-(CH_2)n_1-CR^{2a}R^{2b}-(CH_2)n_2$ - wherein n1 and n2 are each 0, R^{2a} represents a hydrogen atom, and R^{2b} represents optionally substituted C₁₋₆ alkyl, carboxyl, C₁₋₄ alkoxycarbonyl, cyano, -(C=O)-N(-R^{2c})(-R^{2d}) wherein R^{2c} and R^{2d} are as defined in formula (I), or optionally substituted phenyl.

[0042] A still further example of more preferred group (iv) represented by X is that R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents $-(CH_2)n_1-CR^{2a}R^{2b}-(CH_2)n_2$ - wherein n1 is an integer of 0 to 3, n2 is 0, and R^{2a} and R^{2b} represent a halogen atom.

[0043] Another example of more preferred group (iv) represented by X is that R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents $-NH-(CH_2)q_1-CR^{4a}R^{4b}-(CH_2)q_2$ - wherein q1 and q2 are each an integer of 0 to 2, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.

[0044] Still another example of more preferred group (iv) represented by X is that R¹ represents a hydrogen atom, Q6 represents a bond, and Q7 represents a bond.

[0045] In formulae (I) and (Ia), an example of preferred group (v) represented by X is that Q8 represents alkylene having 1 to 3 carbon atoms or alkenylene having 2 or 3 carbon atoms; Q9 represents -O-, -NH-, or -S(=O)r- wherein r is an integer of 0 to 2; and Q10 represents a bond, alkylene having 1 or 2 carbon atoms or alkenylene having 2 carbon atoms and the alkylene and alkenylene represented by Q10 are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl.

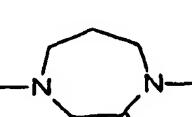
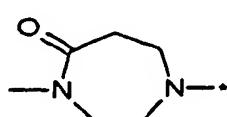
[0046] In formulae (I) and (Ia), an example of preferred group (vi) represented by X is that Q11 represents a bond, a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom, or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom; and Q12 represents a bond, $-(CH_2)s-CHR^5-$, wherein s is an integer of 0 or 1, R⁵ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, $-(CH_2)t-NR^6-$, wherein t is an integer of 0 or 1, R⁶ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, or $-NH-(CH_2)u-CHR^7-$ wherein u is an integer of 0 or 1, and R⁷ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.

[0047] In formulae (I) and (Ia), an example of preferred group (vii) represented by X is that Q13 represents a bond, a saturated carbocyclic group optionally substituted by an oxygen atom, or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom; Q14 represents a bond, $-(CH_2)v-CHR^8-$, wherein v is an integer of 0 or 1, R⁸ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, $-(CH_2)w-NR^9-$, wherein w is an integer of 0 or 1, R⁹ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, or $-NH-(CH_2)x-CHR^{10}$ - wherein x is an integer of 0 or 1 and R¹⁰ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.

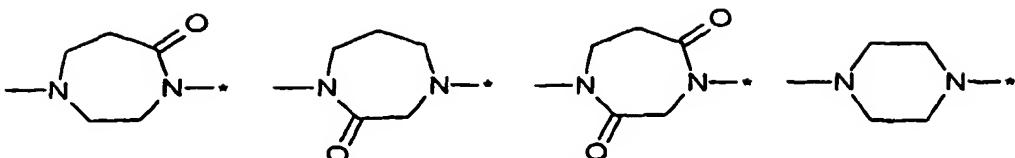
[0048] In formulae (I) and (Ia), an example of preferred group (viii) represented by X is that Q15 represents a five- to seven-membered saturated heterocyclic group which is optionally substituted by an oxygen atom and contains two nitrogen atoms, more preferably a piperazine ring or a homopiperazine ring; and y is 1 or 2.

[0049] In formulae (I) and (Ia), an example of preferred group (ix) represented by X is that Q16 represents a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom, or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom; and z is 1 or 2.

[0050] In formulae (I) and (Ia), preferably, "five- to seven-membered saturated heterocyclic group" represented by Q6 in group (iv), Q11 in group (vi), Q13 in group (vii), Q15 in group (viii), and Q16 in group (ix) represent any one of the following groups:



5



[0051] When Q6 in group (iv) represents the above group, the bond with * represents a bond to Q7 and the bond without * represents a bond to group -N(-R¹)-.

[0052] When Q11 in group (vi) represents the above group, the bond with * represents a bond to Q12, and the bond without * represents a bond to group -O-.

[0053] When Q13 in group (vii) represents the above group, the bond with * represents a bond to Q14, and the bond without * represents a bond to group Het.

[0054] When Q15 in group (viii) represents the above group, the bond with * represents a bond to -(CH₂)y-, and the bond without * represents a bond to -C(=O)-.

[0055] When Q16 in group (ix) represents the above group, the bond with * represents a bond to -(CH₂)z-, and the bond without * represents a bond to -N(-R¹)-.

[0056] In formulae (I) and (Ia), the five- to seven-membered monocyclic saturated or unsaturated carbocyclic group represented by Z is preferably phenyl, cyclohexyl, norpyranyl, or norbornanyl.

[0057] In formulae (I) and (Ia), phenyl represented by Z is preferably substituted at the 2- and 6-positions, at the 3- and 4-positions, or at the 2-, 4-, and 6-positions.

[0058] In formulae (I) and (Ia), the five- to seven-membered saturated or unsaturated monocyclic carbocyclic or heterocyclic group represented by Z is preferably a five- to seven-membered saturated or unsaturated heterocyclic group containing one nitrogen atom and/or one oxygen atom, more preferably furanyl, pyridyl, piperidyl, pyrrolidinyl, pyronyl, isoxazoyl, morphonyl, or imidazoyl.

[0059] In formulae (I) and (Ia), the five- to seven-membered saturated or unsaturated monocyclic carbocyclic or heterocyclic group represented by Z is preferably a five- to seven-membered saturated or unsaturated heterocyclic group containing two nitrogen atoms, more preferably imidazoyl.

[0060] In formulae (I) and (Ia), the five- to seven-membered saturated or unsaturated monocyclic carbocyclic or heterocyclic group represented by Z is preferably a five- to seven-membered saturated or unsaturated heterocyclic group containing one sulfur atom, more preferably thieryl.

[0061] In formulae (I) and (Ia), the nine- to twelve-membered bicyclic saturated or unsaturated carbocyclic group represented by Z is preferably a nine- to ten-membered bicyclic unsaturated carbocyclic group, more preferably naphthyl, naphthalenyl, or indenyl.

[0062] In formulae (I) and (Ia), the nine- to twelve-membered bicyclic saturated or unsaturated heterocyclic group represented by Z is preferably a nine- to ten-membered unsaturated bicyclic heterocyclic group containing one nitrogen atom and/or one or two oxygen atoms, more preferably indolyl, 1,3-benzodioxole, quinolyl, quinazolyl, isoquinolyl, 3,4-methylenedioxophenyl, benzo[6]furanyl, sinolyl, indazolyl, benzimidazolyl, benzotriazolyl, or phthalazinyl.

[0063] In formulae (I) and (Ia), the thirteen- to fifteen-membered tricyclic saturated or unsaturated carbocyclic or heterocyclic group represented by Z is preferably fluorenyl, phenothiazinyl, carbazolyl, or phenoazinyl.

[0064] Examples of preferred compounds represented by formula (I) and preferred compounds represented by formula (Ia) according to the present invention include:

(1) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (i) wherein Q1 represents a bond, alkylene having 1 to 3 carbon atoms, or alkenylene having 2 or 3 carbon atoms and the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

(2) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-

1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

5 X represents group (ii) wherein Q2 represents a bond, alkylene having 1 to 3 carbon atoms, or alkenylene having 2 or 3 carbon atoms and the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

10 (3) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

15 X represents group (iii) wherein Q3 represents alkylene having 1 or 2 carbon atoms or alkenylene having 2 carbon atoms, Q4 represents -O-, -NH-, or -S(=O)m- wherein m is an integer of 0 to 2, and Q5 represents a bond, alkylene having 1 or 2 carbon atoms, or alkenylene having 2 carbon atoms and the alkylene and alkenylene represented by Q5 represents C₁₋₄ alkyl or optionally substituted phenyl, and

20 Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

25 (4) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

30 X represents group (iv) wherein R¹ represents a hydrogen atom or C₁₋₄ alkylcarbonyl, Q6 represents a bond, a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, and Q7 represents a bond; -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 is an integer of 0 or 1, n2 is 0, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl; -(CH₂)p-NR³- wherein p is an integer of 0 or 1 and R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl; or -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2- wherein q1 is 0 or 1, q2 is 0, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, and

35 Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

40 (4') compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

45 X represents group (iv) wherein R¹ represents a hydrogen atom or C₁₋₄ alkylcarbonyl, Q6 represents a bond, a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, and Q7 represents a bond; -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 and n2 are each an integer of 0 to 3, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, optionally substituted C₁₋₆ alkyl, carboxyl, C₁₋₄ alkoxy carbonyl, cyano, -(C=O)-N(-R^{2c})(-R^{2d}), wherein R^{2c} and R^{2d}, which may be the same or different, represent a hydrogen atom, optionally substituted C₁₋₄ alkyl, optionally substituted C₁₋₄ alkoxy, cyclopropyl, or optionally substituted benzyl, or optionally substituted phenyl; -(CH₂)p-NR³- wherein p is an integer of 0 or 1 and R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl; -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2- wherein q1 and q2 are each an integer of 0 to 2, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl or optionally substituted phenyl; -(C=O)-O-CR^{4a}R^{4b}-CH₂- wherein R^{4a} represents a hydrogen atom and R^{4b} represents a hydrogen atom, optionally substituted C₁₋₆ alkyl, or optionally substituted phenyl; -NH-(CH₂)i-NH- wherein i is an integer of 1 to 4; or -S(=O)_j- wherein j is 0, 1, or 2, and

50 Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

55 (5) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc),

or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (v) wherein Q8 represents alkylene having 1 to 3 carbon atoms or alkenylene having 2 or 3 carbon atoms, Q9 represents -O-, -NH-, or -S(=O)r- wherein r is an integer of 0 to 2, and Q10 represents a bond, alkylene having 1 or 2 carbon atoms, or alkenylene having 2 carbon atoms and the alkylene and alkenylene represented by Q10 are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

(6) compound wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (vi) wherein Q11 represents a bond, a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom, or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom, and Q12 represents a bond; -(CH₂)_s-CHR⁵- wherein s is an integer of 0 or 1 and R⁵ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl; -(CH₂)_t-NR⁶- wherein t is an integer of 0 or 1 and R⁶ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl; or -NH-(CH₂)_u-CHR⁷- wherein u is an integer of 0 or 1 and R⁷ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

(7) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (vii) wherein Q13 represents a bond, a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom, or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom, and Q14 represents a bond; -(CH₂)_v-CHR⁸- wherein v is an integer of 0 or 1 and R⁸ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl; -(CH₂)_w-NR⁹- wherein w is an integer of 0 or 1 and R⁹ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl; or -NH-(CH₂)_x-CHR¹⁰- wherein x is an integer of 0 or 1 and R¹⁰ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

(8) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (viii) wherein Q15 represents a five- to seven-membered saturated heterocyclic group which is optionally substituted by an oxygen atom and contains two nitrogen atoms, more preferably a piperazine ring or a homopiperazine ring, and y is 1 or 2, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted; and

(9) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (ix) wherein Q16 represents a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and z is 1 or 2, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted.

Further examples of preferred compounds represented by formula (I) and preferred compounds represented by formula (Ia) according to the present invention include:

(10) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl or 5-isoquinolyl,

X represents group (iv) wherein R¹ represents a hydrogen atom, Q₆ represents a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom, and Q₇ represents -(CH₂)_p-NR³- wherein p is an integer of 0 or 1 and R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl; or -NH-(CH₂)_{q1}-CR^{4a}R^{4b}-(CH₂)_{q2}- wherein q1 is 0 or 1, q2 is 0, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

(11) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (iv) wherein R¹ represents a hydrogen atom, Q₆ represents a five- to seven-membered saturated heterocyclic group which is optionally substituted by an oxygen atom and contains one nitrogen atom, and Q₇ represents -(CH₂)_{n1}-CR^{2a}R^{2b}-(CH₂)_{n2}- wherein n1 is an integer of 0 or 1, n2 is 0, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

(12) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl or 5-isoquinolyl,

X represents group (iv) wherein R¹ represents a hydrogen atom, Q₆ represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, and Q₇ represents -(CH₂)_{n1}-CR^{2a}R^{2b}-(CH₂)_{n2}- wherein n1 and n2, which may be the same or different, are each an integer of 0 to 3, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, or optionally substituted C₁₋₄ alkyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

(13) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl 1H-5-indazolyl 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (iv) wherein R¹ represents a hydrogen atom, Q₆ represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, and Q₇ represents -(CH₂)_{n1}-CR^{2a}R^{2b}-(CH₂)_{n2}-, wherein n1 and n2 are 0, R^{2a} represents a hydrogen atom, and R^{2b} represents optionally substituted C₁₋₆ alkyl, carboxyl, C₁₋₄ alkoxy carbonyl, cyano, -(C=O)-N(-R^{2c})(-R^{2d}), wherein R^{2c} and R^{2d} are as defined in formula (I), or optionally substituted phenyl, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted;

(14) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or

(IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (iv) wherein R¹ represents a hydrogen atom, Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, and Q7 represents -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 represents an integer of 0 to 3, n2 is 0, and R^{2a} and R^{2b} represent a halogen atom, and

Z represents a halogen atom;

(15) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (iv) wherein R¹ represents a hydrogen atom, Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, and Q7 represents -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2- wherein q1 and q2 are each an integer of 0 to 2, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl,

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted; and

(16) compounds wherein Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc), or alternatively Het represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj), preferably 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl,

X represents group (iv) wherein R¹ represents a hydrogen atom, Q6 represents a bond, and Q7 represents a bond, and

Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted.

[0065] Examples of preferred compounds according to the present invention include compounds prepared in Examples 1 to 322.

[0066] Examples of particularly preferred compounds according to the present invention include the following compounds. The number within parentheses represents working example numbers:

- (40) (20) N-[1-(4-bromophenyl)ethyl]-N'-(1,3-dioxy-2,3-dihydro-1H-5-isoindolyl)urea;
- (21) N-(1-benzyl-3-piperidyl)-N(1H-5-indazolyl)-amine;
- (22) N-[1-(4-bromobenzyl)-4-piperidyl]-N-(1H-5-imidazolyl)amine;
- (80) N-(2,6-dichlorobenzyl)-N'-(4-pyridyl)urea;
- (83) N-(2-chloro-6-fluorobenzyl)-N'-(1,3-dioxy-2,3-dihydro-1H-6-isoindolyl)urea;
- (90) N-(2,6-difluorobenzyl)-N'-(1,3-dioxy-2,3-dihydro-1H-5-isoindolyl)urea;
- (95) N-(2,6-difluorobenzyl)-N'-(1H-5-indazolyl)-urea;
- (102) N-(2-chloro-6-fluorobenzyl)-N'-(1H-5-indazolyl)urea;
- (126) N-(1-benzyl-4-piperidyl)-N-(1H-5-indazolyl)-amine;
- (127) N-(1-benzyl-4-piperidyl)-N-(1H-5-indazolyl)-amine hydrochloride;
- (128) N-(1H-5-indazolyl)-N-(4-piperidyl)amine;
- (146) N-(1-benzyl tetrahydro-1H-pyrrolyl)-N-(1H-5-indazolyl)amine;
- (164) N-[1-(4-fluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine;
- (221) methyl 2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetate;
- (227) N1-(2-fluoroethyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide;
- (240) N-(1H-5-indazolyl)-N-[1-(2-methyl-1-phenylpropyl)-3-piperidyl]amine;
- (243) N1-(1H-5-indazolyl)-N4-propyl-1,4-cyclohexanediamine;
- (246) N1-(2-fluoroethyl)-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine;
- (247) N1-cyclopropyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine;

- (248) N1-(1H-5-indazolyl)-1,4-cyclohexanediamine;
 (259) N1-(1H-5-indazolyl)-N4-phenylethyl-1,4-cyclohexanediamine;
 (260) N1-(5-isoquinolyl)-N4-propyl-1,4-cyclohexanediamine;
 (261) N1-(2-fluoroethyl)-N4-(5-isoquinolyl)-1,4-cyclohexanediamine;
 (262) N1-cyclopropyl-N4-(5-isoquinolyl)-1,4-cyclohexanediamine;
 (273) N-(5-isoquinolyl)-N-[1-(4,4,4-trifluorobutyl)-3-piperidyl]amine;
 (281) N-(1H-5-indazolyl)-N-[1-(2-methylpentyl)-3-piperidyl]amine;
 (282) N-(1H-5-indazolyl)-N-[1-(2,4,6-trifluorobenzyl)-3-piperidyl]amine;
 (286) N-(1H-5-indazolyl)-N-(1-propyl-4-piperidyl)-amine;
 (287) N-[1-(cyclopropylmethyl)-4-piperidyl]-N-(1H-5-indazolyl)amine;
 (289) N-[1-(3-fluoropropyl)-4-piperidyl]-N-(1H-5-indazolyl)amine;
 (290) N-(1H-5-indazolyl)-N-[1-(3,3,3-trifluoropropyl)-4-piperidyl]amine;
 (293) N-[1-(2-chloro-4-fluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine;
 (294) methyl 2-(3,4-difluoropentyl)-2-[3-(1H-5-indazolylamino)piperidino]acetate;
 (298) N-(1H-5-indazolyl)-N-[1-[4-(trifluoromethyl)-benzyl]-3-piperidyl]amine;
 (300) N-[1-(3,4-difluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine;
 (318) N-(5-isoquinolyl)-N-(1-propyl-4-piperidyl)-amine;
 (320) N-[1-(2-ethylbutyl)-4-piperidyl]-N-(5-isoquinolyl)amine; and
 (322) N-[1-(3-fluoropropyl)-4-piperidyl]-N-(5-isoquinolyl)amine.

[0067] Pharmaceutically acceptable salts of the compounds represented by formula (I) and the compounds represented by formula (Ia) include acid addition salts. Acid addition salts include: salts with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid, and nitric acid; salts with organic acids such as maleic acid, fumaric acid, malic acid, oxalic acid, tartaric acid, succinic acid, citric acid, acetic acid, lactic acid, methanesulfonic acid, p-toluenesulfonic acid and salicylic acid; and salts with amino acids such as lysine. These acid addition salts may be converted to corresponding free bases by a conventional method, for example, by a reaction with an alkali such as sodium hydroxide or potassium hydroxide. Further, the compounds may be brought to quaternary ammonium salts or salts with metals such as sodium, potassium, calcium, magnesium, or aluminum.

[0068] Pharmaceutically acceptable solvates of the compounds represented by formula (I) and the compounds represented by formula (Ia) include hydrates.

[0069] In the compounds represented by formula (I) and the compounds represented by formula (Ia), optical isomers, racemic forms thereof, and cis/trans isomers may exist, and the compounds according to the present invention include all of these isomers. These isomers may be isolated according to a conventional method, or may be produced using various materials for respective isomers.

Production of compounds

[0070] The compounds represented by formula (I) and the compounds represented by formula (Ia) according to the present invention may be produced according to schemes 1 to 11 below.

- [0071]** Compounds, wherein X represents group (i), may be produced according to schemes 1 and 2.
[0072] Compounds, wherein X represents group (ii) or (iii), may be produced according to scheme 3.
[0073] Compounds, wherein X represents group (iv), may be produced according to schemes 4, 5, 6, and 7.
[0074] Compounds, wherein X represents group (v), may be produced according to scheme 8.
[0075] Compounds, wherein X represents group (vi), may be produced according to scheme 9.
[0076] Compounds, wherein X represents group (vii), may be produced according to scheme 10.
[0077] Compounds, wherein X represents group (viii), may be produced according to scheme 11.
[0078] Compounds, wherein X represents group (ix), may be produced according to scheme 11.

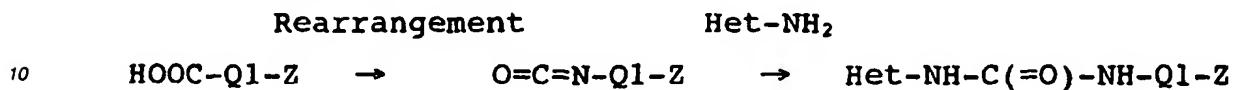
Scheme 1

heating



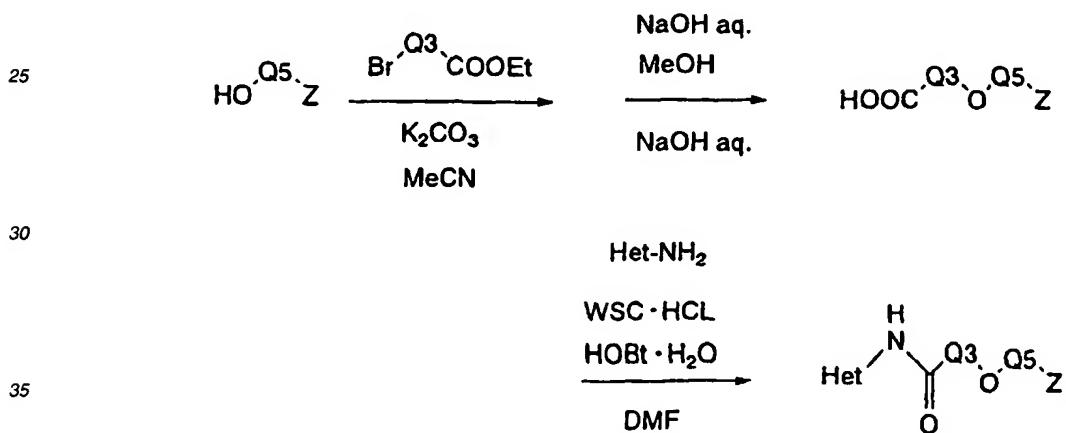
[0079] Compounds, wherein X represents group (i), can be produced by adding an isocyanate derivative O=C=N-Q1-Z, wherein Z is as defined above, to an amine derivative Het-NH₂, wherein Het is as defined above, in a suitable solvent, such as toluene or N,N-dimethylformamide, and heating the mixture. When there is no suitable aniline derivative, an aniline compound can be produced by catalytically reducing a corresponding nitro compound.

5

Scheme 2

[0080] An isocyanate compound is produced by reacting a carboxylic acid derivative Z-Q1-COOH, wherein Z is as defined above, with diphenylphosphoryl azide in a suitable solvent, for example, toluene or N,N-dimethylformamide, in the presence of a base, for example, triethylamine. The compound, wherein X represents group (i), can be produced by reacting the isocyanate compound thus obtained with an amino derivative Het-NH₂ wherein Het is as defined above. When there is no suitable aniline derivative, an aniline compound can be produced by catalytically reducing a corresponding nitro compound.

20

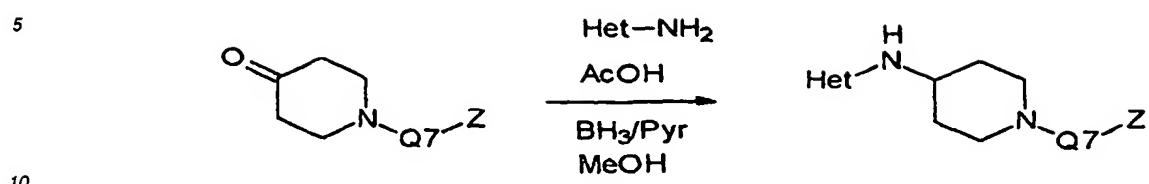
Scheme 3

40 [0081] A carbocyclic acid compound can be produced by reaction of a phenol derivative Z-OH, wherein Z is as defined above, with Br-Q3-COOEt, wherein Q3 is as defined above, for example, ethyl bromocarbonate, in the presence of a base, for example, potassium carbonate, followed by hydrolysis. Next, the compound, wherein X represents formula (iii) wherein Q4 represents -O-, can be produced by adding a condensing agent to the carboxylic acid compound thus obtained in a suitable solvent, for example, N,N-dimethylformamide, and reacting the mixture with an amino derivative Het-NH₂ wherein Het is as defined above.

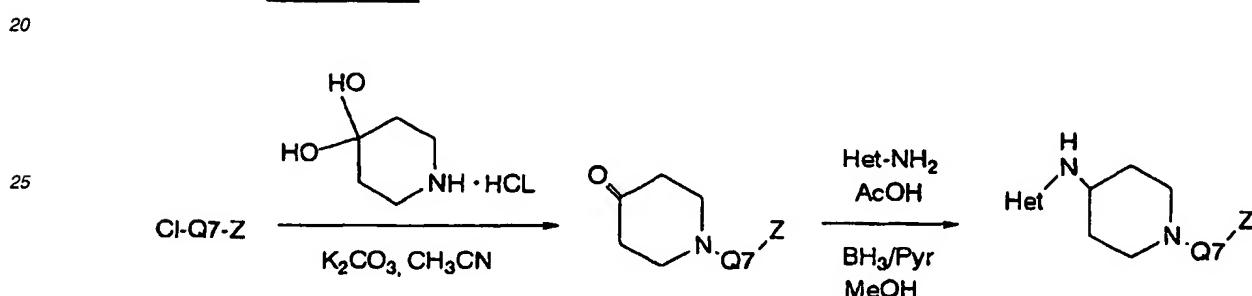
45 [0082] The compounds, wherein Q4 represents -NH- or -S(=O)m-, can be produced by reacting an amino derivative Het-NH₂, wherein Het is as defined above, with a carboxylic acid derivative Z-Q5-Q4-Q3-COOH, wherein Z and Q2 are as defined above, in a suitable solvent, for example, N,N-dimethylformamide, in the presence of a condensing agent.

50 [0083] The compounds, wherein X represents group (ii), can be produced by reacting an amino derivative Het-NH₂, wherein Het is as defined above, with a carboxylic acid derivative Z-Q2-COOH, wherein Z and Q2 are as defined above, in a suitable solvent, for example, N,N-dimethylformamide, in the presence of a condensing agent.

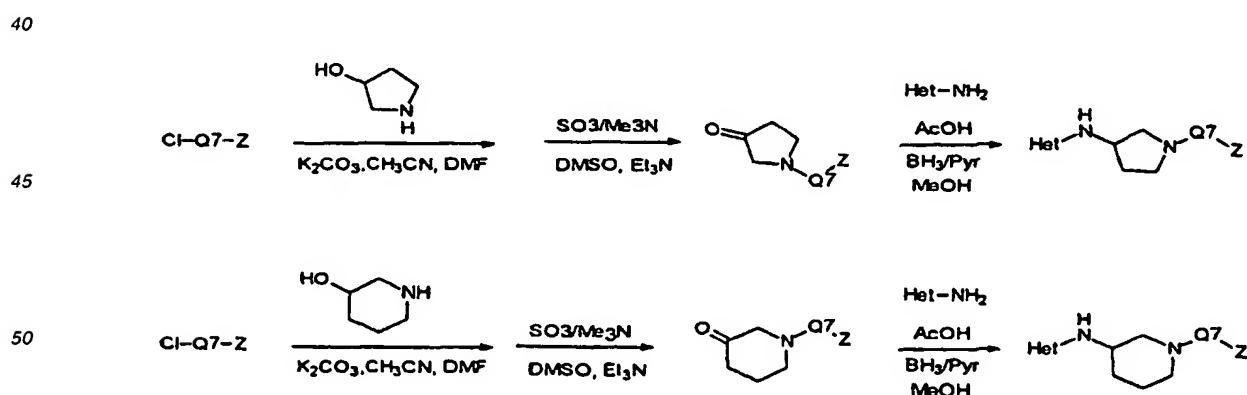
55

Scheme 4

[0084] The compounds, wherein X represents group (iv) wherein Q6 represents piperidine, can be produced by condensing a 4-piperidone derivative and an amino derivative Het-NH₂, wherein Het is as defined above, for example, 5-aminoindazole, in a suitable solvent, for example, methanol, with an acid to form an imine compound and then reducing the imine compound with a borane-pyridine complex.

Scheme 5

[0085] The compounds, wherein X represents group (iv) wherein Q6 represents piperidine, can be produced by reacting 4-piperidone monohydrate with Cl-Q7-Z, wherein Q7 and Z are as defined above, for example, benzyl chloride, in the presence of a base, for example, potassium carbonate, to give an N-benzyl compound, adding an amino derivative Het-NH₂, wherein Het is as defined above, for example, 5-aminoindazole, and condensing the mixture with an acid to form an imine compound, and reducing the imine compound with a borane-pyridine complex.

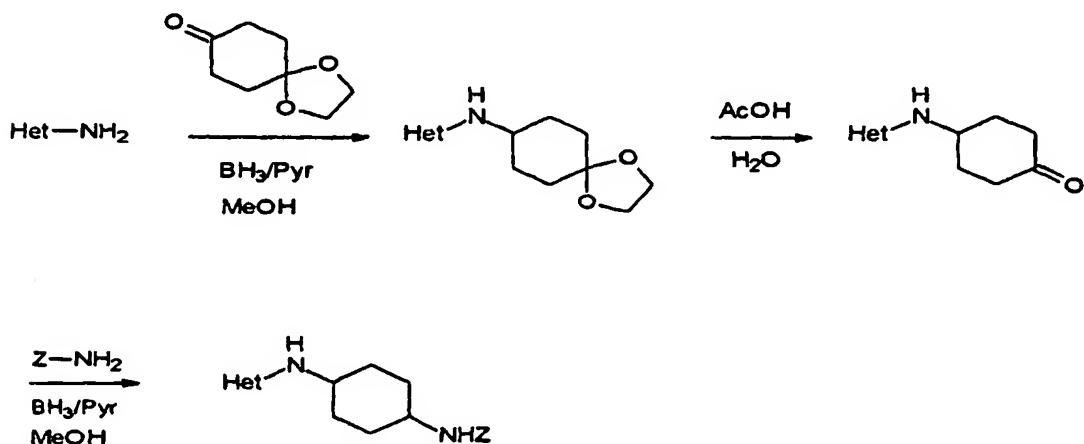
Scheme 6

[0086] The compounds, wherein X represents group (iv), wherein Q6 represents pyrrolyl, can be produced by first reacting (R)-(-)-3-pyrrolidinol hydrochloride with Cl-Q7-Z, wherein Q7 and Z are as defined above, for example, benzyl chloride, in the presence of a base, for example, potassium carbonate, to give an N-benzyl compound, dissolving triethylamine in anhydrous dimethyl sulfoxide, adding a sulfur trioxide-trimethylamine complex at room temperature in an argon atmosphere, and oxidizing the N-benzyl compound in this system to give an intermediate, then reacting this

intermediate with an amino derivative $\text{Het}-\text{NH}_2$, wherein Het is as defined above, for example, 5-aminoindazole, performing condensation with an acid to form an imine compound, and then reducing the imine compound with a borane-pyridine complex.

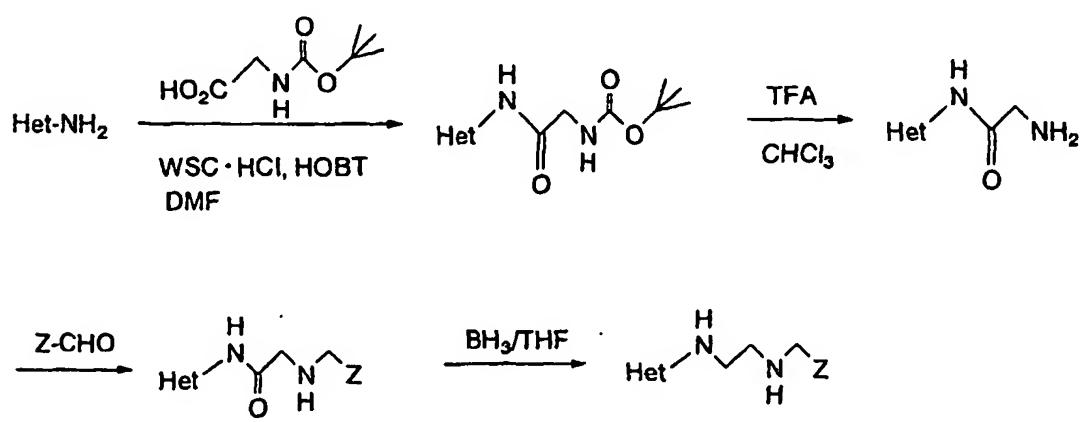
[0087] The compounds, wherein X represents group (iv) wherein $\text{Q}6$ represents piperidyl, can be produced in the same manner as described above.

Scheme 7



[0088] The compounds, wherein X represents group (iv) wherein $\text{Q}6$ represents cyclohexyl, can be produced by dissolving 1,4-cyclohexanediene monoethylene ketal and an amino derivative $\text{Het}-\text{NH}_2$, wherein Het is as defined above, for example, 5-aminoindazole, in a suitable solvent, for example, methanol, condensing the solution with acetic acid to give an imine compound, reducing the imine compound with a borane-pyridine complex at room temperature to give an amino compound as an intermediate, then dissolving the amino compound as the intermediate in acetic acid-water, stirring the solution at 70 to 100°C, preferably about 80°C, to give a ketone compound, reacting the ketone compound with a suitable amino compound $Z-\text{NH}_2$, wherein Z is as defined above, performing condensation with an acid to give an imine compound, and then reducing the imine compound with a suitable reducing agent, for example, a borane-pyridine complex.

Scheme 8



[0089] 2-[(Tert-butoxycarbonyl)amino]acetic acid and $\text{Het}-\text{NH}_2$, wherein Het is as defined above, for example, 5-aminoindazole, are dissolved in dimethylaminopyridine and dimethylformamide, and N-[3-(diethylamino)propyl]-N'-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole were added to the solution obtained at 0 to 25°C, preferably about 0°C. The reaction mixture is stirred at room temperature to give an amide compound.

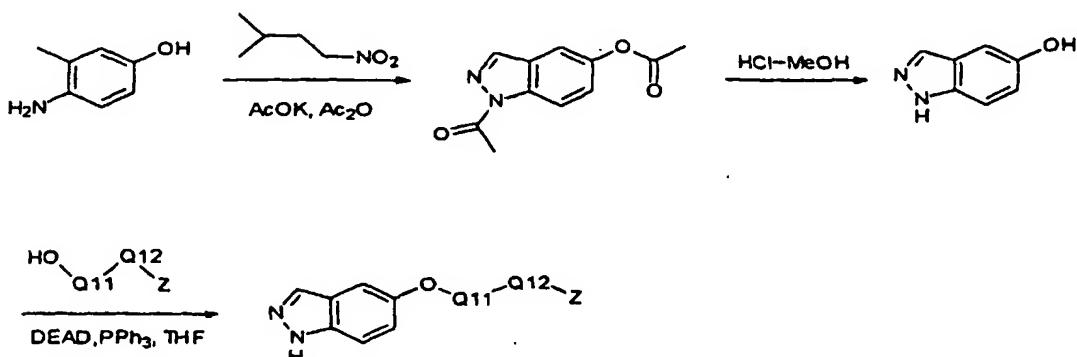
[0090] The compounds, wherein X represents group (v), wherein $\text{Q}8$ and $\text{Q}10$ represent methylene and $\text{Q}9$ represents -NH-, can be produced by removing the protective group in the amide compound with trifluoroacetic acid, then

reacting the deprotected compound with benzaldehyde, condensing the reaction product with acetic acid to form an imine compound, reducing the imine compound with sodium triacetoxyborohydride to give an amine compound, and then reducing the amine compound with a borane-pyridine complex. Compounds, wherein Q8 and Q10 represent a group other than methylene, can be produced in the same manner as described above.

5

Scheme 9

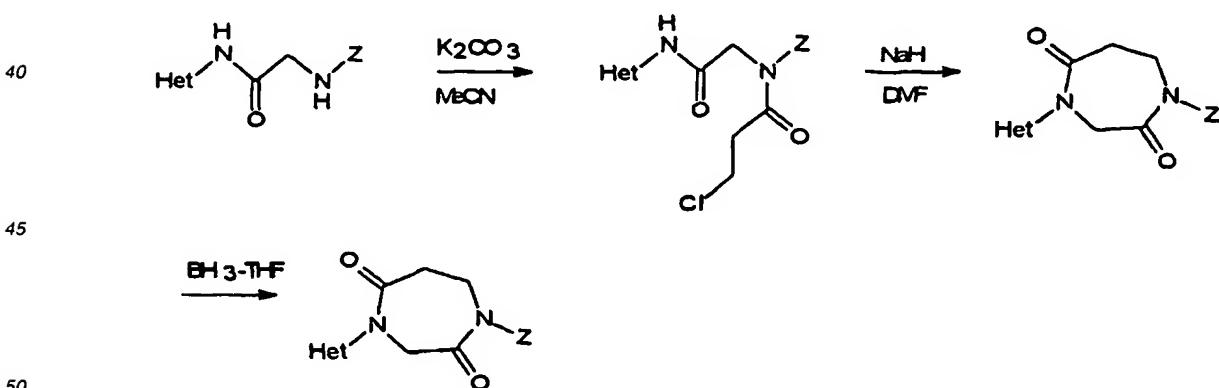
10



25 [0091] 4-Amino-m-cresol is suspended in acetic anhydride and chlorobenzene in the presence of potassium acetate, isoamyl nitrate is added to the suspension at 70°C to 100°C, preferably about 80°C, and the mixture is stirred to form an indazole skeleton. The intermediate thus obtained is dissolved in hydrochloric acid-methanol, and the mixture is preferably stirred at room temperature to deacetylate the compound.

30 [0092] The compounds, wherein X represents group (vi), can be produced by dissolving this deacetylated compound, HO-Q11-Q12-Z, for example, 1-benzyl-4-hydroxypiperidine, and triphenylphosphine in tetrahydrofuran to prepare a solution and reacting the solution with diethyl azodicarboxylate at room temperature. Compounds other than the compounds indicated in the scheme can be produced by reacting Het-OH with HO-Q11-Q12-Z in the same manner as described above.

35

Scheme 10

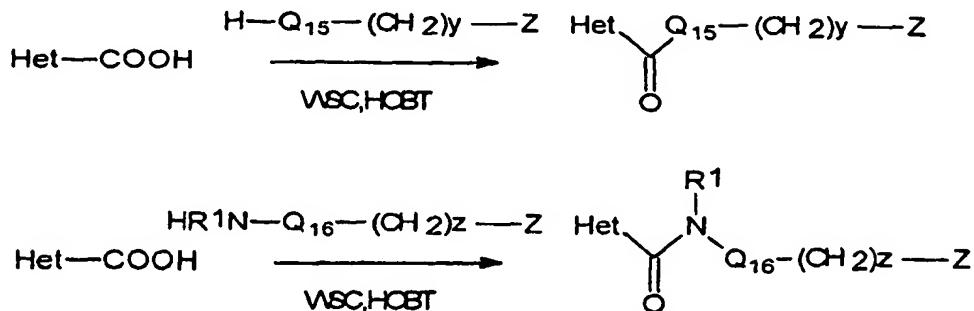
55 [0093] A tertiary amine compound is produced by reacting the final product produced according to scheme 8 with 3-chloropropionyl chloride in a suitable solvent, for example, acetonitrile or N,N-dimethylformamide, in the presence of a base, for example, potassium carbonate. A ring-closed compound is produced by stirring the tertiary amine thus obtained in a suitable solvent, for example, N,N-dimethylformamide, in the presence of a base, for example, sodium hydride, at 70°C to 100°C, preferably 80°C. The compounds, wherein X represents formula (vii), can be produced by dissolving the ring-closed product thus obtained in tetrahydrofuran, adding a borane-tetrahydrofuran complex to the solution under ice cooling, for example, at 0°C to 25°C, preferably 0°C, and raising the temperature of the mixture, for

example, to 25°C to 80°C, preferably 60°C, to perform reduction.

[0094] The compounds produced according to schemes 1 to 11 can be if necessary separated from the reaction mixture and purified, for example, by recrystallization or chromatography.

5

Scheme 11



10

15

[0095] The compounds represented by formula (I), wherein X represents group (viii) or (ix), can be produced by reacting a carboxylic acid derivative: Het-COOH with an amine derivative: H-Q15-(CH₂)_y-Z or HR¹N-Q16-(CH₂)_z-Z in the presence of a condensing agent.

Use of compounds

[0096] The compounds represented by formulae (I) and (Ia) have Rho kinase inhibitory activity (see Pharmacological Test Example 1). Therefore, the compounds represented by formulae (I) and (Ia) can be used in the treatment of diseases mediated by Rho kinase. Diseases mediated by Rho kinase include hypertension, asthma including bronchial asthma, angina pectoris, cerebrovascular spasm, peripheral circulatory disorder, threatened premature birth, glaucoma, constriction of visual field, pollakiuria, cancer, invasion/metastasis of cancer, arteriosclerosis, retinopathy, immune response, inflammation, autoimmune diseases, cerebral dysfunction, osteoporosis, microbism, chronic renal failure, chronic nephritis, diabetic nephropathy, IgA nephropathia, thrombosis-related diseases, rheumatism, impotence, and fibrosis.

[0097] According to the present invention, there is provided a method for treating diseases mediated by Rho kinase, comprising the step of administering the compound represented by formula (Ia) together with a pharmaceutically acceptable carrier, to a mammal.

[0098] According to the present invention, there is also provided use of the compound represented by formula (Ia), for the manufacture of a medicament for the treatment of diseases mediated by Rho kinase.

40

[0099] It has been clarified that Rho is activated upon the receipt of signals from various cell membrane acceptors and the activated Rho plays a role in the contraction of smooth muscle through ROCK/Rho kinase and, further, actomyosin system (K. Kimura et al., Science, Vol. 273, No. 5272, pp 245-248 (1996); and Kureishi et al., J. Biol. Chem., Vol. 272, No. 19, pp 12257-60 (1997)). The contraction of smooth muscle is deeply involved in the pathology of hypertension, angina pectoris, cerebrovascular spasm, asthma, peripheral circulatory disorder, threatened premature birth, glaucoma, constriction of visual field, impotence, pollakiuria, and the like (for example, hypertension: AP. Samlyo et al., Rev. Physiol. Biochem. Pharmacol., Vol. 134, pp 209-34 (1999), angina pectoris: Shimokawa et al., Cardiovasc. Res., Vol. 43, No. 4, pp 1029-39 (1999); and Satoh, H., & Kawahara, K: Jpn. J. Pharmacol., 79 (suppl): 211P, 1999, cerebrovascular contraction: Motohiko Sato and Kohzo Kaibuchi: Abstract of the 57th Annual Meeting of the Japan Neurosurgical Society: 153, 1998; N. Ono et al., Pharmacol. Ther., Vol. 82, No. 2-3, pp 123-31(1991); and Shimokawa et al., Cardiovasc. Res., Vol. 43, No. 4, pp 1029-39 (1999), impotence: Andersson, K. E. & Stief, C. G. & World J. Urol. 15, 14-20 (1997)).

[0100] For hypertension, ROCK/Rho kinase inhibitors have antihypertensive activity in spontaneously hypertensive rats (SHR), renal hypertensive rats, and deoxycorticosterone acetate-salt rats (DOCA-salt rats) (Uehata, M., Ishizaki, T. et al.: Nature, 389: 990-994, 1997).

[0101] For asthma, ROCK/Rho kinase inhibitors have bronchodilation activity and antiasthmatic activity in extirpated bronchia or bronchial asthma model animals (WO 93/05021 and WO 95/28387). Further, Rho kinase inhibitors suppress an increase in bronchial resistance caused by acetylcholine inhalation in bronchial asthma models in a dose-dependent

manner and suppress, in vitro, chemotaxis caused by PAF in eosinophilic leukocytes of human peripheral blood in a concentration-dependent manner (Kunihiro Iitsuka: Arerugi (Allergy), 47: 943, 1998, Kunihiro Iitsuka and Akihiro Yoshii: Journal of The Japanese Respiratory Society, 37: 196, 1999). Further, Rho kinase is also involved in migration of leukocytes.

- 5 [0102] For impotence, ROCK/Rho kinase inhibitors have corpus cavernosum penis relaxation activity in vitro and have corpus cavernosum penis pressure rising activity in vivo (Kanchan Chitaley et al., Nature Medicine, Vol. 7, No. 1, 119-122 (2001)).
- 10 [0103] Compounds represented by formula (I) and compounds represented by formula (Ia) according to the present invention actually have leukocyte migration inhibitory activity and blood pressure depression activity (see Pharmacological Test Examples 2 and 5).
- 15 [0104] Therefore, the compounds represented by formula (I) and the compounds represented by formula (Ia) according to the present invention can be used in the treatment of hypertension, asthma including bronchial asthma, angina pectoris, cerebrovascular contraction, peripheral circulatory disorder, threatened premature birth, glaucoma, constriction of visual field, impotence, pollakiuria and other diseases.

Cancer, metastasis of cancer, etc.

- 20 [0105] Rho is activated upon the receipt of signals from various cell membrane receptors, and the activated Rho functions, through ROCK/Rho kinase and, further, actomyosin system, as a molecular switch of cellular phenomena such as cell movement, cell adhesion, alteration of cytoplasm (formation of actin stressed fibers), control of cell division (sthenia of cytokinesis or activation of gene transcription), cell proliferation, sthenia of carcinogenesis and invasion of cancer and the like (P. Keely et al., Trends Cell Biol. Vol. 8, No. 3, pp 101-6 (1998); and K. Itoh et al., Nat. Med., Vol. 5, No. 2, pp 221-5 (1999)).
- 25 [0106] Cell movement plays an important role in invasion/metastasis of cancer, arteriosclerosis, retinopathy, immune response and the like. Cell adhesion is deeply involved in metastasis of cancer, inflammation, and autoimmune diseases. The change in character of cells is deeply involved in cerebral dysfunction, osteoporosis, microbism and the like. Cell proliferation is deeply involved in cancer, arteriosclerosis and the like (Jikken Igaku (Experimental Medicine), Vol. 17, No. 7 (1999)).
- 30 [0107] In particular, for transformation of cells to malignant state and metastasis/invasion of cancer, Rho is involved in the control of morphology of cells and, in addition, in cell proliferation, particularly in the progression of cell cycle from gap1 period (G1 phase) to synthesis period (S phase) (Yamamoto, M., Marui, N., Oncogene, 8: 1449-1455, 1993). Further, it has been found that oncogenes such as Dbl are GDP-GTP exchange factors for Rho family (Hart, M. J., Eva, A., Nature, 354: 311-314, 1991). Further, it has been found that Rac and Rho are activated downstream of information transmission of Ras (Ridley, A. J. & Hall, A.: Cell, 70: 401-410, 1992). Further, it has been demonstrated that Rac and Rho are possibly involved in the transformation of cells to malignant state by Ras downstream of Ras (Qui, R. G., Chen, J., et al.: Nature, 374: 457-459, 1995., Qui, R. G., Chen, J., et al.: Proc. Natl. Acad. Sci. USA, 92: 11781-11785, 1995, and Khosravi-Far, R., Solski, P. A.: Mol. Cell. Biol., 15: 6443-6453, 1995). Furthermore, it has been proven by ROCK/Rho kinase inhibitor (Y-27632) that the path from Rho to ROCK is involved in transformation to malignant state (Sahai, E., Ishizaki, T.: Curr. Biol., 9: 136-145, 1999).
- 40 [0108] Further, it has been reported in various cell systems that, as with leukocytes, cell movement in cancer invasion is regulated by an actomyosin system as a moving device and an intracellular signal transfer system for controlling the actomyosin system and Rho family protein regulates cytoskeleton protein and controls various cell functions such as alteration of morphology, adhesion, movement, division, transfer regulation and the like of cells (K. Itoh et al., Nat. Med., Vol. 5, No. 2, pp 221-5 (1999); P. Keely et al., Trends Cell Biol. Vol. 8, No. 3, pp 101-6 (1998)).
- 45 [0109] It has also been reported that ROCK downstream of Rho controls invasive movement through the activation of an actomyosin system (Yoshioka, K., Matsumura, F.: J. Biol. Chem., 273: 5146-5154, 1998). It has been demonstrated that controlling the path from Rho to ROCK by ROCK/Rho kinase inhibitor (Y-27632) suppresses the invasive movement (Itoh, K., Yoshioka, K.: Nature Med., 5: 221-225, 1999).
- 50 [0110] Therefore, the compounds represented by formula (I) and the compounds represented by formula (Ia) according to the present invention can be used in the treatment of cancer, invasion/metastasis of cancer, arteriosclerosis, retinopathy, immune response, inflammation, autoimmune diseases, cerebral dysfunction, osteoporosis, and microbism.

Renal diseases

- 55 [0111] Renal disorder was found in Rho GDI knockout mouse (Oncogene, 1999; 18 (39): 5373-80).
- [0112] Further, as described above, Rho is activated upon the receipt of signals from various cell membrane receptors, and the activated Rho is involved in cell adhesion or migration of leukocytes through ROCK/Rho kinase and

actomyosin system. Cell adhesion and migration of leukocytes are involved in inflammation, particularly nephritis (Osamu Fujimoto and Kohzo Kaibuchi, Journal of The Japanese Society of Internal Medicine, 1999; 88 (1); 148-54).

[0113] Furthermore, Rho is involved in nephritis through HGF, oxidized LDL, platelets, or Na-H exchange (Mol. Cell. Biol. 1995; 15 (2): 1110-22; J. Biol. Chem. 1999; 274 (43): 30361-4; J. Biol. Chem., 1999; 274 (40): 28293-300; and EMBO J., 1998; 17 (16): 4712-22).

[0114] The compounds represented by formula (I) and the compounds represented by formula (Ia) according to the present invention actually have albuminuria amelioration activity (see Pharmacological Test Examples 3 and 4).

[0115] Therefore, the compounds represented by formula (I) and the compounds represented by formula (Ia) according to the present invention can be used in the treatment of chronic renal failure, chronic nephritis, diabetic nephropathy, and IgA nephropathia.

Inflammation, thrombosis-related diseases, etc.

[0116] It has been known that Rho is activated upon the receipt of signals from various cell membrane receptors, and the activated Rho functions, through Rho kinase and, further, actomyosin system, as a molecular switch of cellular phenomena such as platelet aggregation, leukocyte aggregation, and leukocyte migration (K. Naka et al., Blood, Vol. 90, No. 10, pp 3736-42 (1997)). Platelet aggregation, leukocyte aggregation, and leukocyte migration are deeply involved in thrombus, inflammation, fibrosis and the like.

[0117] The compounds represented by formula (I) and the compounds represented by formula (Ia) actually have leukocyte migration inhibitory activity (see Pharmacological Test Example 2).

[0118] Therefore, the compounds represented by formula (I) and the compounds represented by formula (Ia) according to the present invention can be used in the treatment of inflammation, asthma, thrombosis-related diseases, for example, cardiac infarction, cerebral infarction, arteriosclerosis obliterans, thrombus obstruction, and generalized angiocoagulation syndrome, rheumatism, and fibrosis.

[0119] Pharmaceutical compositions comprising the compounds of the present invention as active ingredient can be administered to a human and a non-human animal orally or parenterally by administration routes, for example, intravenous administration, intramuscular administration, subcutaneous administration, rectal administration, or percutaneous administration. Therefore, the pharmaceutical composition comprising the compound according to the present invention as active ingredient may be formulated into suitable dosage forms according to the administration routes.

[0120] Specifically, oral preparations include tablets, capsules, powders, granules, syrups, pills, and troches, and parenteral preparations include injections, such as solutions and suspensions, inhalants, suppositories, transdermal preparations, for example, tapes, ointments, eye drops, and eye ointments.

[0121] These various preparations may be prepared by conventional methods, for example, with commonly used component, such as excipients, disintegrants, binders, lubricants, colorants, diluents, corrigents, flavors, emulsifiers, and solubilizers.

[0122] Excipients include, for example, lactose, glucose, corn starch, sorbit, and crystalline cellulose. Disintegrants include, for example, starch, sodium alginate, gelatin powder, calcium carbonate, calcium citrate, and dextrin. Binders include, for example, dimethylcellulose, polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum arabic, gelatin, hydroxypropylcellulose, and polyvinyl pyrrolidone. Lubricants include, for example, talc, magnesium stearate, polyethylene glycol, and hydrogenated vegetable oils.

[0123] In the formulation of solid preparations, additives are used such as sucrose, lactose, cellulose sugar, D-mannitol, maltitol, dextran, starches, agar, alginates, chitins, chitosans, pectins, tragacanths, gum arabics, gelatins, collagens, caseins, albumin, calcium phosphate, sorbitol, glycine, carboxymethylcellulose, polyvinyl pyrrolidone, hydroxypropylcellulose, hydroxypropyl-methylcellulose, glycerin, polyethylene glycol, sodium hydrogencarbonate, magnesium stearate, and talc. Further, tablets may be those on which, if necessary, conventional coating has been provided, for example, sugar coated tablets, enteric coated tablets, film coated tablets, or two-layer tablets, and multilayer tablets.

[0124] In the formulation of semi-solid preparations, vegetable fats and oils, such as olive oils, corn oils, and castor oils, mineral fats and oils, such as petrolatum, white petrolatum, and hard paraffin, waxes, such as jojoba oils, carnauba wax, and beeswax, and partially synthesized or wholly synthesized glycerin fatty acid esters, such as laurylic acid, myristic acid, and palmitic acid, may be used. Examples of commercially available products thereof include Witepsol manufactured by Dynamid Nobel and Pharmasol manufactured by Nippon Oils & Fats Co., Ltd.

[0125] In the formulation of solutions, additives may be used such as sodium chloride, glucose, sorbitol, glycerin, olive oil, propylene glycol, and ethyl alcohol. In the formulation of injections, aseptic aqueous solutions, for example, physiological saline, isotonic solutions, oily solutions, for example, sesame oils and soybean oils, may be used. If necessary, suitable suspending agents, for example, sodium carboxymethylcellulose, nonionic surfactants, solubilizers, for example, benzyl benzoate, benzyl alcohol and the like may be used in combination with the above solutions.

[0126] In the formulation of eye drops, aqueous liquid preparations or aqueous solutions are used, and, in particular, aseptic aqueous solutions for injections may be used. Various additives, such as buffers, preferably, for example, borate

buffers, acetate buffers, and carbonate buffers for abatement of stimulation, isotonicity, solubilizers, preservatives, thickening agents, chelating agents, pH adjustors for adjusting pH preferably to about 2 to 8.5, and aromatics, may be properly added to the liquid preparation for eye drops.

[0127] The content of the compound according to the present invention in the pharmaceutical composition may vary according to the dosage form. The content is, however, generally about 0.1 to 100% by weight, preferably about 1 to 50% by weight, based on the whole composition.

[0128] The dose may be appropriately determined in consideration of various conditions, for example, the age, weight, sex, type of disease, and severity of condition of patients, and the preparation may be administered, for example, in an amount of about 1 to 500 mg. This dose may be administered at a time daily or divided doses of several times daily.

EXAMPLES

[0129] The present invention is further illustrated by the following examples that are not intended as a limitation of the invention.

Example 1: N-(4-Pyridyl)-N'-(2,4,6-trichlorophenyl)urea

[0130] 4-Aminopyridine (500 mg, 3.56 mmol) and 2,4,6-trichlorophenyl isocyanate (503.6 mg, 3.56 mmol 1.0 moleg), were dissolved in toluene, and the mixture was then stirred at 110°C for 3 hr.

[0131] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was then washed with ether to give the title compound as a colorless crystal (819 mg, 86.6%).

MS m/z: 315

¹H-NMR δ: 7.43 (2H, dd, J = 1.7, 4.9 Hz), 7.62 (2H, s), 8.35 (2H, dd, J = 1.7, 4.9 Hz), 8.48 (1H, s), 9.45 (1H, S)

Example 2: N1-(4-Pyridyl)-2-(2,6-dibromo-4-fluorophenoxy)acetamide

[0132] Potassium carbonate (614.4 mg, 4.44 mmol) and methyl bromoacetate (0.4 ml, 4.08 mmol) were added to a solution of 2,6-dibromo-4-fluorophenol (1 g, 3.70 mmol) in acetonitrile, and the mixture was stirred at 80°C for 3 hr.

[0133] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give an ester compound as a colorless crystal.

[0134] A 10% aqueous sodium hydroxide solution was added to an ethanol solution of the ester compound, and the mixture was stirred at an external temperature of 80°C for one hr.

[0135] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a carbonyl compound as a colorless crystal (1.12 g, 87.6%).

MS m/z: 266 ¹H-NMR δ: 4.59 (2H, s), 7.29 (1H, s), 7.30 (1H, s)

[0136] 4-Aminopyridine (50 mg, 0.53 mmol) and WSC · HCl (126.2 mg, 0.64 mmol) and HOBr · H₂O (86.1 mg, 0.64 mmol) were added to a solution of carboxyl compound (191.6 mg, 0.58 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.

[0137] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (122.4 mg, 86.6%).

MS m/z: 404

¹H-NMR δ: 4.66 (2H, s), 7.34 (2H, s), 7.16 (1H, s), 7.58 (2H, dd, J = 1.7, 4.6 Hz), 8.57 (2H, dd, J = 1.5, 4.9 Hz)

Example 3: N1-(4-Pyridyl)-2-(2,6-dichlorophenoxy)-acetamide

[0138] Potassium carbonate (1.02 g, 7.36 mmol) and methyl bromoacetate (1.12 g, 6.75 mmol) were added to a solution of 2,6-dichlorophenol (1 g, 6.13 mmol) in acetonitrile, and the mixture was stirred at 80°C for 3 hr.

[0139] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give an ester compound as a colorless crystal.

[0140] A 10% aqueous sodium hydroxide solution was added to an ethanol solution of the ester compound, and the mixture was stirred at an external temperature of 80°C for one hr.

[0141] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a carboxyl compound as a colorless crystal (1.08 g, 79.4%).

[0142] 4-Aminopyridine (50 mg, 0.53 mmol), WSC·HCl (118.8 mg, 0.60 mmol), and HOBt·H₂O (86.1 mg, 0.60 mmol) were added to a solution of carboxyl compound (129.1 mg, 0.58 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.

[0143] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (15.5 mg, 10.0%).

15 MS m/z: 297

¹H-NMR δ: 3.74 (2H, d, J = 2.7 Hz, CH₂), 7.24 - 7.30 (3H, m, Ar-H)

Example 4: N1-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-2'-(2,6-dichloro-4-fluorophenyl)acetamide

20 [0144] Potassium carbonate and methyl bromoacetate were added to a solution of 2,6-dichloro-4-fluorophenol in acetonitrile, and the mixture was stirred at 80°C for 3 hr.

[0145] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a colorless crystal.

[0146] A 10% aqueous sodium hydroxide solution was added to an ethanol solution of the ester compound, and the mixture was stirred at an external temperature of 80°C for one hr.

[0147] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a carboxyl compound as a colorless crystal.

[0148] 4-Aminophthalimide (100 mg, 0.62 mmol), WSC·HCl (146.5 mg, 0.74 mmol), and HOBt·H₂O (100 mg, 0.74 mmol) were added to a solution of carboxyl compound (162.1 mg, 0.68 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.

[0149] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (40.1 mg, 17.0%).

40 MS m/z: 383

¹H-NMR δ: 4.68 (2H, s), 7.61 (2H, dd, J = 1.2, 8.3 Hz), 7.78 (1H, d, J = 8.1 Hz), 8.01 (1H, dd, J = 1.7, 8.1 Hz), 8.01 (1H, dd, J = 1.7, 8.1 Hz), 8.23 (1H, d, J = 2.0 Hz), 10.70 (1H, s), 11.25 (1H, s)

Example 5: N1-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-2'-(2,6-dichlorophenoxy)acetamide

45 [0150] Potassium carbonate and methyl bromoacetate were added to a solution of 2,6-dichlorophenol in acetonitrile, and the mixture was stirred at 80°C for 3 hr.

[0151] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give an ester compound as a colorless crystal.

[0152] A 10% aqueous sodium hydroxide solution was added to an ethanol solution of the ester compound, and the mixture was stirred at an external temperature of 80°C for one hr.

[0153] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a carboxyl compound as a colorless crystal.

[0154] 4-Aminophthalimide (100 mg, 0.62 mmol), WSC-HCl (146.5 mg, 0.74 mmol), and HOBr·H₂O (100 mg, 0.74 mmol) were added to a solution of carboxyl compound (149.9 mg, 0.68 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.

[0155] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (63.7 mg, 28.3%).

MS m/z: 365

¹⁰ ¹H-NMR δ: 4.71 (2H, s), 7.24 (1H, t, J = 8.5 Hz), 7.54 (1H, d, J = 8.1 Hz), 7.54 (1H, d, J = 8.1 Hz), 7.80 (1H, d, J = 8.3 Hz), 8.02 (1H, dd, J = 2.0, 8.1 Hz), 8.24 (1H, d, J = 2.0 Hz), 10.70 (1H, s), 11.245 (1H, s)

Example 6: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(2,4,6-trichlorophenyl)urea

[0156] 5-Aminophthalimide (100 mg, 0.62 mmol) and 2,4,6-trichlorophenyl isocyanate (150.9 mg, 0.68 mmol) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0157] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was washed with n-hexane to give the title compound as a colorless crystal (143.0 mg, 60.4%).

MS m/z: 384

¹⁰ ¹H-NMR δ: 7.74 (2H, d, J = 20.0 Hz), 7.77 (2H, s), 8.03 (1H, s), 8.52 (1H, s), 9.69 (1H, s), 11.13 (1H, s)

Example 7: N1-(4-Pyridyl)-(E)-3-(2,6-dichlorophenyl)-2-propeneamide

[0158] 4-Aminopyridine (50 mg, 0.53 mmol), WSC-HCl (126.3 mg, 0.58 mmol), and HOBr·H₂O (500 mg, 0.58 mmol) were added to a solution of 2,6-dichlorocinnamic acid (126.8 mg, 0.58 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.

[0159] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (81.9 mg, 52.6%).

MS m/z: 293

¹⁰ ¹H-NMR δ: 6.94 (1H, d, J = 16.1 Hz), 7.32 (1H, t, J = 8.1 Hz), 7.48 (2H, d, J = 8.1 Hz), 7.75 (2H, dd, J = 1.5, 4.9 Hz), 7.86 (1H, d, J = 16.1 Hz), 8.42 (2H, dd, J = 1.7, 4.9 Hz)

Example 8: N-(2,6-Difluorophenyl)-N'-(4-pyridyl)urea

[0160] 4-Aminopyridine (100 mg, 1.06 mmol) and 2,6-difluorophenyl isocyanate (181.3 mg, 1.17 mmol) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0161] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was washed with n-hexane to give the title compound as a colorless crystal (249.3 mg, 94.3%).

MS m/z: 249

¹⁰ ¹H-NMR δ: 6.95 (1H, d, J = 8.3 Hz), 6.97 (1H, d, J = 8.1 Hz), 7.19 (1H, t, J = 8.3 Hz), 7.48 (2H, dd, J = 1.5, 5.1 Hz), 8.31 (2H, dd, J = 1.5, 4.9 Hz)

Example 9: N-(2,6-Dichlorophenyl)-N'-(4-pyridyl)urea

[0162] 4-Aminopyridine (100 mg, 1.06 mmol) and 2,6-dichlorophenyl isocyanate (219.7 mg, 1.17 mmol) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0163] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was washed with n-hexane to give the title compound as a colorless crystal (262.2 mg, 87.5%).

MS m/z: 282

¹⁰ ¹H-NMR δ: 7.20 (1H, t, J = 7.8 Hz), 7.39 (2H, d, J = 8.3 Hz), 7.49 (2H, dd, J = 1.7, 4.9 Hz), 8.31 (2H, dd, J = 1.5, 5.1 Hz)

Example 10: N-(2,6-Diisopropylphenyl)-N'-(4-pyridyl)urea

[0164] 4-Aminopyridine (100 mg, 1.06 mmol) and 2,6-diisopropylphenyl isocyanate (216.0 mg, 1.06 mmol) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0165] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and

the residue was washed with n-hexane to give the title compound as a colorless crystal (94.3 mg, 29.9%).

MS m/z: 297

¹H-NMR (500 MHz) δ: 1.21 (12H, s), 3.16 - 3.22 (2H, m), 7.19 (2H, d, J = 8.0 Hz), 7.30 (1H, t, J = 7.9 Hz), 7.49 (2H, d, J = 6.1 Hz), 8.30 (2H, d, J = 6.1 Hz)

5

Example 11: N-(4-Methoxyphenyl)-N'-(4-pyridyl)urea

[0166] 4-Aminopyridine (100 mg, 1.06 mmol) and 4-methoxyphenyl isocyanate (158.5 mg, 1.06 mmol) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0167] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was washed with n-hexane to give the title compound as a colorless crystal (223.7 mg, 86.4%).

MS m/z: 243

¹H-NMR δ: 3.77 (3H, s), 6.87 (2H, dd, J = 2.1, 6.8 Hz), 7.32 (2H, dd, J = 2.1, 6.8 Hz), 7.50 (2H, dd, J = 1.5, 5.1 Hz), 8.30 (2H, dd, J = 1.5, 5.1 Hz)

15

Example 12: N-(2,4-Dichlorophenyl)-N'-(4-pyridyl)urea

[0168] 4-Aminopyridine (100 mg, 1.06 mmol) and 2,4-dichlorophenyl isocyanate (219.7 mg, 1.17 mmol, 1.1 eq) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0169] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was washed with n-hexane to give the title compound as a colorless crystal (279.6 mg, 93.3%).

MS m/z: 282

¹H-NMR δ: 7.31 (1H, dd, J = 2.4, 9.0 Hz), 7.48 (1H, d, J = 2.4 Hz), 7.53 (2H, dd, J = 1.7, 4.9 Hz), 8.17 (1H, d, J = 9.0 Hz), 8.33 (2H, dd, J = 1.7, 4.9 Hz)

25

Example 13: N-(2,6-Dichlorophenyl)-N'-(1H-5-indazolyl)-urea

[0170] 5-Aminoindazole (100 mg, 0.75 mmol) and 2,6-dichlorophenyl isocyanate (155.3 mg, 0.83 mmol, 1.1 eq) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0171] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was washed with n-hexane to give the title compound as a purple crystal (232.6 mg, 96.5%).

MS m/z: 321

¹H-NMR δ: 7.29 (1H, d, J = 8.8 Hz), 7.33 (1H, dd, J = 1.7, 8.8 Hz), 7.45 (1H, d, J = 8.8 Hz), 7.52 (1H, d, J = 8.8 Hz), 7.89 (1H, dd, J = 1.7, 8.8 Hz), 7.96 (1H, S), 8.14 (1H, s), 8.86 (1H, s)

35

Example 14: N1-(1H-5-Indazolyl)-2-(2,6-dichlorophenoxy)-acetamide

[0172] Potassium carbonate and methyl bromoacetate were added to a solution of 2,6-dichlorophenol in acetonitrile, and the mixture was then stirred at 80°C for 3 hr.

[0173] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a colorless crystal.

[0174] A 10% aqueous sodium hydroxide solution was added to an ethanol solution of the ester compound, and the mixture was stirred at an external temperature of 80°C for one hr.

[0175] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a carboxyl compound as a colorless crystal.

[0176] 5-Aminoindazole (100 mg, 0.75 mmol), WSC-HCl (178.4 mg, 0.90 mmol), and HOBr·H₂O (121.8 mg, 0.90 mmol) were added to a solution of carboxyl compound (182.6 mg, 0.83 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.

[0177] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (198.5 mg, 78.7%).

MS m/z: 336

¹H-NMR δ: 4.64 (2H, s), 7.23 (1H, t, J = 7.8 Hz), 7.49 (1H, d, J = 8.8 Hz), 7.53 (2H, d, J = 7.8 Hz), 7.53 (2H, dd, J = 1.7, 9.0 Hz), 8.04 (1H, s), 8.17 (1H, s), 10.06 (1H, s), 13.00 (1H, s)

Example 15: N1-(1H-5-Indazolyl)-2-(2,6-dichloro-4-fluorophenoxy)acetamide

- [0178] Potassium carbonate and methyl bromoacetate were added to a solution of 2,6-dichloro-4-fluorophenol in acetonitrile, and the mixture was stirred at 80°C for 3 hr.
- [0179] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a colorless crystal.
- [0180] A 10% aqueous sodium hydroxide solution was added to an ethanol solution of the ester compound, and the mixture was stirred at an external temperature of 80°C for one hr.
- [0181] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a carboxyl compound as a colorless crystal.
- [0182] 5-Aminoindazole (100 mg, 0.75 mmol), WSC-HCl (178.4 mg, 0.90 mmol), and HOBr·H₂O (121.8 mg, 0.90 mmol) were added to a solution of carboxyl compound (197.4 mg, 0.83 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.
- [0183] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (210.2 mg, 79.1%).

MS m/z: 354

¹H-NMR δ: 4.62 (2H, s), 7.49 (1H, t, J = 8.8 Hz), 7.53 (1H, dd, J = 1.7, 8.8 Hz), 7.59 (1H, s), 7.61 (1H, s), 8.03 (1H, s), 8.16 (1H, s), 10.06 (1H, s), 12.99 (1H, s)

Example 16: N1-(1H-5-Indazolyl)-2-(2,4,6-trichlorophenoxy)acetamide

- [0184] Potassium carbonate and methyl bromoacetate were added to a solution of 2,4,6-trichlorophenol in acetonitrile, and the mixture was stirred at 80°C for 3 hr.
- [0185] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give an ester compound as a colorless crystal.
- [0186] A 10% aqueous sodium hydroxide solution was added to an ethanol solution of the ester compound, and the mixture was stirred at an external temperature of 80°C for one hr.
- [0187] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a carboxyl compound as a colorless crystal.
- [0188] 5-Aminoindazole (50 mg, 0.38 mmol), WSC-HCl (89.2 mg, 0.45 mmol), and HOBr·H₂O (60.9 mg, 0.45 mmol) were added to a solution of carboxyl compound (105.4 mg, 0.41 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.
- [0189] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (75.1 mg, 54.1%).

MS m/z: 370

¹H-NMR δ: 4.65 (2H, s), 7.49 (1H, d, J = 8.8 Hz), 7.52 (1H, dd, J = 1.7, 8.8 Hz), 7.75 (2H, s), 8.03 (1H, s), 8.15 (1H, s), 10.08 (1H, s), 12.99 (1H, s)

Example 17: N1-(4-Pyridyl)-2-[(2,6-dichlorophenyl)-sulfanyl]acetamide

- [0190] Potassium carbonate (277.8 mg, 2.01 mmol) and methyl bromoacetate (0.2 ml, 1.84 mmol) were added to a

solution of 2,6-dichlorothiophenol (300 mg, 1.68 mmol) in acetonitrile, and the mixture was stirred at 80°C for 3 hr.
 [0191] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give an ester compound as a colorless crystal.

[0192] A 10% aqueous sodium hydroxide solution (500 mg, 3.56 mmol) was added to an ethanol solution of the ester compound, and the mixture was stirred at an external temperature of 80°C for one hr.

[0193] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform] to give a carboxyl compound as a colorless crystal (360.2 mg, 86.6%).

[0194] 4-Aminopyridine (138.5 mg, 0.58 mmol), WSC·HCl (118.8 mg, 0.60 mmol), and HOBr·H₂O (86.1 mg, 0.60 mmol) were added to a solution of the carboxyl compound (50 mg, 0.53 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 4 hr.

[0195] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a light yellow crystal (26.4 mg, 15.9%).

MS m/z: 313

¹H-NMR δ: 3.74 (2H, d, J = 2.7, CH₂), 7.24 - 7.30 (3H, m, Ar-H)

Example 18: N-(2-Chloro-6-fluorophenyl)-N'-(4-pyridyl)-urea

[0196] Diphenylphosphoryl azide (0.15 ml, 0.69 mmol, 1.2 eq) and triethylamine (0.1 ml, 0.69 mmol, 1.2 eq) were added to a solution of 2-chloro-6-fluorobenzoic acid (100 mg, 0.57 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0197] Thereafter, 4-aminopyridine (64.7 mg, 0.69 mmol, 1.2 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0198] After the completion of the reaction, water and ethyl acetate were added, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (101.5 mg, 66.6%).

MS m/z: 265

¹H-NMR δ: 6.08 (2H, d, J = 5.37 Hz), 6.73 (1H, t, J = 5.37), 7.34 (2H, dd, J = 1.58, 4.88), 7.38 (1H, dd, J = 1.22, 7.32), 7.51 (2H, d, J = 7.81), 8.28 (2H, dd, J = 1.71, 4.88), 8.84 (1H, s)

Example 19: N-Cyclohexyl-N'-(4-pyridyl)urea

[0199] 4-Aminopyridine (100 mg, 1.06 mmol) and cyclohexyl isocyanate (146.3 mg, 1.17 mmol) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0200] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was then washed with n-hexane to give the title compound as a colorless crystal (216 mg, 92.8%).

MS m/z: 219

¹H-NMR δ: 1.13 - 1.36 (5H, m), 1.52 - 1.55 (1H, m), 1.63 - 1.68 (2H, m), 1.78 - 1.82 (2H, m), 3.42 - 3.51 (1H, m), 7.96 (1H, s), 8.14 (1H, s), 8.86 (1H, s)

Example 20: N-[1-(4-Bromophenyl)ethyl]-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0201] 4-Aminophthalimide (100 mg, 0.62 mmol) and 4-bromophenylethyl isocyanate (153.4 mg, 0.68 mmol, 1.0 eq) were dissolved in toluene, and the mixture was then stirred at 110°C for 4 hr.

[0202] After the completion of the reaction, the solvent was removed by distillation under the reduced pressure, and the residue was then washed with n-hexane to give the title compound as a colorless crystal (62.5 mg, 26.1%).

MS m/z: 388

¹H-NMR (500 MHz) δ: 1.21 (12H, s), 3.16 - 3.22 (2H, m), 7.19 (2H, d, J = 8.0 Hz), 7.30 (1H, t, J = 7.9 Hz), 7.49 (2H, d, J = 6.1 Hz), 8.30 (2H, d, J = 6.1 Hz)

Example 21: N-(1-Benzyl-3-piperidyl)-N(1H-5-indazolyl)-amine

[0203] A mixture of 5-Aminoindazole (100 mg, 0.75 mmol), N-benzyl-3-piperidone (186.5 mg, 0.83 mmol), and acetic

acid (one drop) in Methanol (1 ml) was stirred at room temperature for 5 min. A borane-pyridine complex (0.08 ml, 0.83 mmol) was added thereto under ice cooling using methanol as a solvent, and the mixture was stirred at room temperature for 4 hr.

[0204] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (178.7 mg, 77.7%).

MS m/z: 306

¹⁰ ¹H-NMR δ: 1.40 - 1.60 (3H, m), 1.70 - 1.80 (2H, m), 2.10 - 2.50 (4H, m), 3.45 (2H, s), 3.16 - 3.22 (2H, m), 6.75 (2H, dd, J = 2.4, 11.2 Hz), 7.15 - 7.28 (10H, m), 7.78 (1H, d, J = 0.7 Hz)

Formation of salt of compound prepared in Example 21

[0205] The compound prepared in Example 21 was dissolved in hydrochloric acid-methanol, and the mixture was then allowed to stand at room temperature for 18 hr. The resultant white precipitate was then collected by filtration, was washed with methanol which had been cooled in an ice bath, and was dried under the reduced pressure to give the title compound.

Example 22: N-[1-(4-Bromobenzyl)-4-piperidyl]-N-(1H-5-imidazolyl)amine

[0206] Potassium carbonate (180 mg, 1.30, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (100 mg, 0.65 mmol) and 4-bromobenzyl bromide (162.7 mg, 0.65 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

[0207] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0208] 5-Aminoindazole (69.33 mg, 0.52 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (0.8 ml, 0.78 mmol, 1.2 eq) was added to the reaction solution under ice cooling, and the mixture was stirred at room temperature for 4 hr.

[0209] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (131.2 mg, 52.4%).

MS m/z: 385

¹H-NMR δ: 1.43 - 1.46 (2H, m), 2.02 (2H, d, J = 12.0H), 2.12 (2H, t, J = 9.0H), 2.79 (1H, d, J = 9.0 Hz), 2.82 (1H, s), 3.23 - 3.28 (1H, m), 3.43 (2H, s), 6.73 (2H, dd, J = 2.2, 7.8 Hz), 7.15 (1H, d, J = 8.3 Hz), 7.19 (1H, d, J = 1.0 Hz), 7.22 (1H, dd, J = 1.0, 9.5 Hz), 7.38 (2H, dd, J = 1.8, 6.6 Hz), 7.80 (1H, d, J = 1.0 Hz)

Example 23: N-[1-(3-Bromobenzyl)-4-piperidyl]-4-(1H-5-imidazolyl)amine

[0210] Potassium carbonate (180 mg, 1.30, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (100 mg, 0.65 mmol) and 3-bromobenzyl bromide (162.7 mg, 0.65 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

[0211] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0212] 5-Aminoindazole (69.33 mg, 0.52 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (0.8 ml, 0.78 mmol, 1.2 eq) was added to the reaction solution under ice cooling, and the mixture was stirred at room temperature for 4 hr.

[0213] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (47.6 mg, 20.0%).

MS m/z: 385

¹H-NMR δ: 2.18 - 2.25 (4H, m), 3.14 (2H, t, J = 12.0 Hz), 3.59 (2H, d, J = 12.0 Hz), 3.88 - 4.00 (1H, m), 4.32 (2H, s), 7.45 - 7.53 (3H, m), 7.64 (2H, d, J = 8.3 Hz), 7.74 (1H, d, J = 8.8 Hz), 7.92 (1H, s), 8.18 (1H, d, J = 0.7 Hz)

5 Example 24: N1-(4-Pyridyl)-2-(2,6-dichloro-4-fluoro-phenoxy)acetamide

[0214] Potassium carbonate (1.83 g, 13.26 mmol, 1.2 eq) and methyl bromoacetate (1.69 g, 11.05 mmol, 1.0 eq) were added to a solution of 2,6-dichloro-4-fluorophenol (2.0 g, 11.05 mmol) in acetonitrile, and the mixture was stirred at 80°C for one hr.

10 [0215] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give an ester compound as a white crystal (2.66 g, 95.2%).

15 [0216] A 5% aqueous sodium hydroxide solution (20 ml) was added to a solution of the ester compound (2.66 g, 10.51 mmol) in ethanol, and the mixture was stirred at an external temperature of 80°C for one hr.

[0217] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give a carboxyl compound as a colorless crystal (2.31 g, 92.0%).

20 [0218] 4-Aminopyridine (393 mg, 4.18 mmol, 1.0 eq), WSC· HCl (964 mg, 5.02 mmol, 1.2 eq), and HOBr·H₂O (678 mg, 5.02 mmol, 1.2 eq) were added to a solution of the carboxyl compound (1.0 g, 4.18 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 3.5 hr.

25 [0219] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (155 mg, 11.8%).

MS m/z: 314

¹H-NMR δ: 4.63 (2H, s), 7.15 (2H, d, J = 7.81 Hz), 7.59 (2H, dd, J = 1.59, 4.76 Hz), 8.57 (2H, dd, J = 1.46, 4.88 Hz), 8.77 (1H, s)

30 Example 25: N1-(4-Pyridyl)-2-(2,4-dichlorophenyl)-acetamide

[0220] 4-Aminopyridine (230 mg, 2.44 mmol, 1.0 eq), WSC· HCl (470 mg, 2.44 mmol, 1.0 eq), and HOBr·H₂O (330 mg, 2.44 mmol, 1.0 eq) were added to a solution of 2,4-dichlorophenylacetic acid (500 mg, 2.44 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

35 [0221] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (54 mg, 7.9%).

40 MS m/z: 280

¹H-NMR δ: 7.30 (1H, d, J = 1.95 Hz), 7.31 (1H, s), 7.39 (1H, d, 1.95), 7.47 (2H, d, J = 6.21), 7.78 (1H, s), 8.46 (2H, d, J = 6.10)

45 Example 26: Ethyl 3,5-dichloro-4-[2-oxo-2-(4-pyridylamino)ethoxy]benzoate

[0222] Potassium carbonate (1.06 g, 7.66 mmol, 1.2 eq) and methyl bromoacetate (0.98 g, 6.38 mmol, 1.0 eq) were added to a solution of ethyl 3,5-dichloro-4-hydroxybenzoate (1.5 g, 6.38 mmol) in acetonitrile, and the mixture was stirred at 80°C for one hr.

50 [0223] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give an ester compound as a white crystal (1.88 g, 96.0%).

[0224] A 5% aqueous sodium hydroxide solution (10 ml) was added to a solution of the ester compound (1.88 g, 6.12 mmol) in ethanol, and the mixture was stirred at an external temperature of 80°C for one hr.

55 [0225] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give a carboxyl compound of the title compound as a colorless crystal (750 mg, 43.9%).

[0226] 4-Aminopyridine (266 mg, 2.82 mmol, 1.0 eq), WSC·HCl (542 mg, 2.82 mmol, 1.05 eq), and HOBr·H₂O (381 mg, 2.82 mmol, 1.05 eq) were added to a solution of the carboxyl compound (750 mg, 2.69 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 15.5 hr.

[0227] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give an intermediate as a crystal (180 mg, 19.6%).

[0228] Potassium carbonate (24 mg, 0.18 mmol, 1.2 eq) and ethyl iodide (27 mg, 0.18 mmol, 1.2 eq) were added to a solution of the intermediate (50 mg, 0.15 mmol) in dimethylformamide, and the mixture was stirred at an external temperature of 80°C for 3 hr.

[0229] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by a preparative TLC [chloroform/methanol] to give the title compound as a crystal (5 mg, 9.2%).

MS m/z: 369

¹H-NMR δ: 1.41 (3H, t, J = 7.07 Hz), 4.40 (2H, q, J = 7.08 Hz), 4.72 (2H, s), 7.60 (2H, d, J = 6.10 Hz), 8.05 (2H, s), 8.58 (2H, d, J = 5.85 Hz), 8.84 (1H, s)

Example 27: N1-(4-Pyridyl)-2-(2,6-difluorophenyl)-acetamide

[0230] Potassium carbonate (1.40 g, 9.22 mmol, 1.2 eq) and methyl bromoacetate (1.18 g, 7.69 mmol, 1.0 eq) were added to a solution of 2,6-difluorophenol (1.0 g, 7.69 mmol) in acetonitrile, and the mixture was stirred at 80°C for one hr.

[0231] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give an ester compound as a white crystal (1.31 g, 98.5%).

[0232] A 5% aqueous sodium hydroxide solution (10 ml) was added to a solution of the ester compound (1.31 g, 7.53 mmol) in ethanol, and the mixture was stirred at an external temperature of 80°C for one hr.

[0233] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give a carboxyl compound as a colorless crystal (1.39 g, 98.2%).

[0234] 4-Aminopyridine (700 mg, 7.39 mmol, 1.0 eq), WSC·HCl (1.70 g, 8.87 mmol, 1.2 eq), and HOBr·H₂O (1.20 g, 8.87 mmol, 1.2 eq) were added to a solution of the carboxyl compound (1.39 g, 7.39 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 3 hr.

[0235] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (107 mg, 5.4%).

MS m/z: 264

¹H-NMR δ: 4.84 (2H, s), 7.11 - 7.17 (3H, m), 7.60 (2H, dd, J = 1.59, 4.76 Hz), 8.44 (2H, dd, J = 1.46, 4.88 Hz),

10.48 (1H, s)

Example 28: N1-(4-Pyridyl)-2-(2,4,6-trifluorophenoxy)-acetamide

[0236] Potassium carbonate (2.12 g, 16.21 mmol, 1.2 eq) and methyl bromoacetate (2.07 g, 13.50 mmol, 1.0 eq) were added to a solution of 2,4,6-trifluorophenol (2.0 g, 13.50 mmol) in acetonitrile, and the mixture was stirred at 80°C for 1.5 hr.

[0237] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give an ester compound as a white crystal (2.76 g, 92.9%).

[0238] A 5% aqueous sodium hydroxide solution (10 ml) was added to a solution of the ester compound (2.76 g, 12.55 mmol) in ethanol, and the mixture was stirred at an external temperature of 80°C for one hr.

[0239] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give a carboxyl compound as a colorless crystal (2.15 g, 83.3%).

[0240] 4-Aminopyridine (457 mg, 4.85 mmol, 1.0 eq), WSC·HCl (1.12 g, 5.83 mmol, 1.2 eq), and HOBr·H₂O (0.79 g, 5.83 mmol, 1.2 eq) were added to a solution of the carboxyl compound (1.0 g, 4.85 mmol) in dimethylformamide,

and the mixture was stirred at room temperature for 3 hr.

[0241] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (73 mg, 5.4%).

MS m/z: 282

¹H-NMR δ: 4.80 (2H, s), 7.27 (2H, t, J = 9.03 Hz), 7.60 (2H, dd, J = 1.59, 4.76 Hz), 8.44 (2H, dd, J = 1.57, 4.77 Hz), 10.47 (1H, s)

10 Example 29: N1-(4-Pyridyl)-2-(2,6-difluoro-4-propionylphenoxy)acetamide

[0242] Sodium hydride (77 mg, 3.22 mmol, 1.5 eq) and methyl bromoacetate (329 mg, 2.15 mmol, 1.0 eq) were added to a solution of 3,5-difluoro-4-hydroxypropiophenol (400 mg, 2.15 mmol) in DMF, and the mixture was stirred at 80°C for one hr.

[0243] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give an ester compound as a colorless crystal (390 mg, 70.4%).

[0244] A 5% aqueous sodium hydroxide solution (5 ml) was added to a solution of the ester compound (390 mg, 1.51 mmol) in ethanol, and the mixture was stirred at an external temperature of 80°C for one hr.

[0245] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give a carboxyl compound as a colorless crystal (280 mg, 75.9%).

[0246] 4-Aminopyridine (40 mg, 0.41 mmol, 1.0 eq), WSC·HCl (94 mg, 0.49 mmol, 1.2 eq), and HOBr·H₂O (66 mg, 0.49 mmol, 1.2 eq) were added to a solution of the carboxyl compound (100 mg, 0.41 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0247] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (17 mg, 13.0%).

MS m/z: 321

¹H-NMR δ: 1.23 (3H, t, J = 7.20 Hz), 2.94 (2H, q, J = 7.16 Hz), 4.82 (2H, s), 7.58 (2H, dd, J = 1.59, 4.76 Hz), 7.62 (2H, d, J = 4.64), 8.58 (2H, d, J = 6.03 Hz), 8.66 (1H, s)

35 Example 30: N1-(4-Pyridyl)-2-(2,6-dichloro-4-methylphenoxy)acetamide

[0248] Potassium carbonate (1.40 g, 10.17 mmol, 1.2 eq) and methyl bromoacetate (1.30 g, 8.47 mmol, 1.0 eq) were added to a solution of 2,6-difluoro-4-cresol (1.50 g, 8.47 mmol) in acetonitrile, and the mixture was stirred at 80°C for one hr.

[0249] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give an ester compound as a colorless crystal (1.85 g, 98.4%).

[0250] A 5% aqueous sodium hydroxide solution (5 ml) was added to a solution of the ester compound (1.85 g, 8.34 mmol) in ethanol, and the mixture was stirred at an external temperature of 80°C for one hr.

[0251] After the completion of the reaction, the reaction solution was concentrated, and the residue was acidified with a 5% aqueous hydrochloric acid solution and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give a carboxyl compound as a colorless crystal (1.21 g, 71.6%).

[0252] 4-Aminopyridine (230 mg, 2.46 mmol, 1.0 eq), WSC· HCl (570 mg, 2.96 mmol, 1.2 eq), and HOBr·H₂O (400 mg, 2.96 mmol, 1.2 eq) were added to a solution of the carboxyl compound (500 mg, 2.46 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0253] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a colorless crystal (60 mg, 7.8%).

MS m/z: 310

¹H-NMR δ: 2.36 (3H, s), 4.64 (2H, s), 7.17 (2H, d, J = 0.49 Hz), 7.59 (2H, dd, J = 1.58, 4.76 Hz), 8.57 (2H, dd, J = 1.57, 4.75 Hz), 8.89 (1H, s)

Example 31: N1-(4-Pyridyl)-2-cyclohexylacetamide

[0254] 4-Aminopyridine (66 mg, 0.70 mmol, 1.0 eq), WSC·HCl (162 mg, 0.85 mmol, 1.2 eq), and HOBr·H₂O (114 mg, 0.85 mmol, 1.2 eq) were added to a solution of cyclohexylacetic acid (100 mg, 0.70 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0255] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (23 mg, 15.0%).

MS m/z: 218

¹H-NMR δ: 0.91 - 1.20 (2H, m), 1.10 - 1.26 (3H, m), 1.56 - 1.80 (6H, m), 2.22 (2H, d, J = 7.08 Hz), 7.55 (2H, dd, J = 1.46, 4.64 Hz), 8.39 (2H, d, J = 6.10 Hz), 10.21 (1H, s)

Example 32: N1-(1H-Pyrazolo[3,4-d]pyrimidin-4-yl)-2-(2,6-dichloro-4-fluorophenoxy)acetamide

[0256] 4-Aminopyrazolo (3,4-d)pyrimidine (61 mg, 0.45 mmol, 1.0 eq), WSC·HCl (104 mg, 0.54 mmol, 1.2 eq), and HOBr·H₂O (73 mg, 0.54 mmol, 1.2 eq) were added to a solution of the carboxyl compound (100 mg, 0.45 mmol), prepared in Example 4, in dimethylformamide, and the mixture was stirred at room temperature for 5 days.

[0257] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (63 mg, 39.1%).

MS m/z: 355

¹H-NMR δ: 4.91 (2H, s), 7.62 (2H, d, J = 8.29 Hz), 8.49 (1H, s), 8.64 (1H, s), 11.25 (1H, s), 13.97 (1H, s)

Example 33: N1-(1H-5-Indazolyl)-1-cyclohexanecarboxyamide

[0258] 5-Aminoindazole (100 mg, 0.75 mmol, 1.0 eq), WSC·HCl (173 mg, 0.90 mmol, 1.2 eq), and HOBr·H₂O (122 mg, 0.75 mmol, 1.2 eq) were added to a solution of cyclohexylcarboxylic acid (96 mg, 0.75 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0259] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (80 mg, 44.0%).

MS m/z: 243

¹H-NMR δ: 1.14 - 1.34 (3H, m), 1.44 (2H, q, J = 11.38 Hz), 1.62 - 1.69 (1H, m), 1.73 - 1.84 (4H, m), 2.33 (1H, tt, J = 3.42, 11.59 Hz), 7.42 (1H, dd, J = 1.46, 9.03 Hz), 7.45 (1H, d, J = 9.03 Hz), 7.98 (1H, s), 8.12 (1H, s), 9.76 (1H, s), 12.92 (1H, s)

Example 34: N1-(1H-5-Indazoyl)-1-cyclohexylacetamide

[0260] 5-Aminoindazole (100 mg, 0.75 mmol, 1.0 eq), WSC·HCl (173 mg, 0.90 mmol, 1.2 eq), and HOBr·H₂O (122 mg, 0.75 mmol, 1.2 eq) were added to a solution of cyclohexylacetic acid (107 mg, 0.75 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0261] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (71 mg, 36.8%).

MS m/z: 257

¹H-NMR δ: 0.92 - 1.04 (2H, m), 1.10 - 1.30 (3H, m), 1.58 - 1.82 (6H, m), 2.19 (2H, d, J = 7.08 Hz), 7.39 (1H, dd, J = 1.71, 9.03 Hz), 7.45 (1H, d, J = 8.78 Hz), 7.98 (1H, s), 8.11 (1H, s), 9.81 (1H, s), 12.92 (1H, s)

Example 35: N1-(1H-5-Indazolyl)-(E)-3-(2-hydroxyphenyl)-2-propeneamide

[0262] 5-Aminoindazole (406 mg, 3.05 mmol, 1.0 eq), WSC·HCl (702 mg, 3.65 mmol, 1.2 eq), and HOBr·H₂O (493

mg, 6.65 mmol, 1.2 eq) were added to a solution of trans-2-coumaric acid (500 mg, 3.05 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0263] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (340 mg, 40.0%).

MS m/z: 279

¹H-NMR δ: 6.87 (1H, t, J = 7.68 Hz), 6.86 (1H, d, J = 15.86), 6.93 (1H, d, J = 8.05), 7.22 (1H, dt, J = 1.71, 8.78 Hz), 7.48 - 7.55 (3H, m), 7.79 (1H, d, J = 15.86 Hz), 8.04 (1H, s), 8.28 (1H, s), 10.17 (1H, s), 12.98 (1H, s)

Example 36: N1-(1H-5-Indazolyl)-(E)-3-(3-hydroxyphenyl)-2-propeneamide

[0264] 5-Aminoindazole (406 mg, 3.05 mmol, 1.0 eq), WSC · HCl (702 mg, 3.65 mmol, 1.2 eq), and HOBr·H₂O (493 mg, 6.65 mmol, 1.2 eq) were added to a solution of trans-3-coumaric acid (500 mg, 3.05 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0265] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (161 mg, 18.9%).

MS m/z: 279

¹H-NMR δ: 6.78 (1H, d, J = 15.61 Hz), 6.82 (1H, dd, J = 2.20, 8.05 Hz), 7.00 (1H, s), 7.05 (1H, d, J = 7.81 Hz), 7.25 (1H, t, J = 7.81 Hz), 7.48 (1H, d, J = 15.61 Hz), 7.51 (2H, s), 8.04 (1H, s), 8.26 (1H, s), 9.65 (1H, s), 10.21 (1H, s), 13.00 (1H, s)

Example 37: N1-(1H-5-Indazolyl)-(E)-3-(4-hydroxyphenyl)-2-propeneamide

[0266] 5-Aminoindazole (406 mg, 3.05 mmol, 1.0 eq), WSC · HCl (702 mg, 3.65 mmol, 1.2 eq), and HOBr·H₂O (493 mg, 6.65 mmol, 1.2 eq) were added to a solution of trans-4-coumaric acid (500 mg, 3.05 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0267] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (318 mg, 37.4%).

MS m/z: 279

¹H-NMR δ: 6.63 (1H, d, J = 15.61 Hz), 6.83 (2H, d, J = 8.54 Hz), 7.45 - 7.51 (5H, m), 8.03 (1H, s), 8.25 (1H, s), 9.92 (1H, s), 10.09 (1H, s), 12.97 (1H, s)

Example 38: N1-(1H-5-Indazolyl)-(E)-3-(3,4-dihydroxyphenyl)-2-propeneamide

[0268] 5-Aminoindazole (406 mg, 3.05 mmol, 1.0 eq), WSC · HCl (702 mg, 3.65 mmol, 1.2 eq), and HOBr·H₂O (493 mg, 6.65 mmol, 1.2 eq) were added to a solution of caffeic acid (550 mg, 3.05 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0269] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (130 mg, 14.4%).

MS m/z: 295

¹H-NMR δ: 6.56 (1H, d, J = 15.61 Hz), 6.78 (1H, d, J = 8.05 Hz), 6.92 (1H, dd, J = 1.95, 8.05 Hz), 7.02 (1H, d, J = 1.95 Hz), 7.40 (1H, d, J = 15.61 Hz), 7.50 (2H, s), 8.03 (1H, s), 8.25 (1H, s), 10.08 (1H, s), 12.97 (1H, s)

Example 39: N1-(1H-5-Indazolyl)-2-(2,4-dinitrophenyl)-acetamide

[0270] 5-Aminoindazole (176 mg, 1.33 mmol, 1.0 eq), WSC · HCl (306 mg, 1.59 mmol, 1.2 eq), and HOBr·H₂O (215 mg, 1.59 mmol, 1.2 eq) were added to a solution of 2,4-dinitrophenylacetic acid (300 mg, 1.33 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0271] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (32 mg, 7.1%).

MS m/z: 341

¹H-NMR δ: 4.30 (2H, s), 7.40 (1H, dd, J = 1.95, 8.78 Hz), 7.49 (1H, d, J = 8.78 Hz), 7.91 (1H, d, J = 8.54 Hz), 7.98 - 8.04 (2H, m), 8.67 (1H, d, J = 1.95 Hz), 8.78 (1H, d, J = 2.44 Hz), 10.30 (1H, s), 12.97 (1H, s)

Example 40: N1-(1H-5-Indazolyl)-(E)-3-(4-hydroxy-3-methoxyphenyl)-2-propeneamide

[0272] 5-Aminoindazole (149 mg, 1.12 mmol, 1.0 eq), WSC · HCl (259 mg, 1.34 mmol, 1.2 eq), and HOBr·H₂O (182 mg, 1.34 mmol, 1.2 eq) were added to a solution of 4-hydroxy-3-methoxycinnamic acid (200 mg, 1.12 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0273] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (158 mg, 45.5%).

MS m/z: 309

¹H-NMR δ: 3.84 (3H, s), 6.66 (1H, d, J = 15.61 Hz), 6.83 (1H, d, J = 8.05 Hz), 7.07 (1H, dd, J = 1.95, 8.05 Hz), 7.19 (1H, d, J = 1.95 Hz), 7.49 (1H, d, J = 15.37 Hz), 7.50 (2H, s), 8.03 (1H, s), 8.26 (1H, s), 9.48 (1H, s), 10.07 (1H, s), 12.96 (1H, s)

Example 41: N1-(1H-5-Indazolyl)-(E)-3-(3-hydroxy-4-methoxyphenyl)-2-propeneamide

[0274] 5-Aminoindazole (149 mg, 1.12 mmol, 1.0 eq), WSC · HCl (259 mg, 1.34 mmol, 1.2 eq), and HOBr·H₂O (182 mg, 1.34 mmol, 1.2 eq) were added to a solution of 3-hydroxy-4-methoxycinnamic acid (200 mg, 1.12 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0275] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (100 mg, 28.8%).

MS m/z: 309

¹H-NMR δ: 3.81 (3H, s), 6.62 (1H, d, J = 15.37 Hz), 6.97 (1H, d, J = 8.05 Hz), 7.04 (1H, dd, J = 1.95, 8.05 Hz), 7.05 (1H, s), 7.44 (1H, d, J = 15.61 Hz), 7.50 (2H, s), 8.03 (1H, s), 8.25 (1H, s), 9.22 (1H, s), 10.09 (1H, s), 12.97 (1H, s)

Example 42: N1-(1H-5-Indazolyl)-(E)-3-(3,4-dimethoxyphenyl)-2-propeneamide

[0276] 5-Aminoindazole (149 mg, 1.12 mmol, 1.0 eq), WSC · HCl (259 mg, 1.34 mmol, 1.2 eq), and HOBr·H₂O (182 mg, 1.34 mmol, 1.2 eq) were added to a solution of 3,4-dimethoxycinnamic acid (234 mg, 1.12 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0277] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (164 mg, 45.2%).

MS m/z: 323

¹H-NMR δ: 3.80 (3H, s), 3.83 (3H, s), 6.73 (1H, d, J = 15.61 Hz), 7.02 (1H, d, J = 8.54), 7.19 (1H, dd, J = 1.95, 8.54 Hz), 7.22 (1H, d, J = 1.95 Hz), 7.51 (2H, s), 7.53 (1H, d, J = 15.86 Hz), 8.03 (1H, s), 8.27 (1H, s), 10.13 (1H, s), 12.92 (1H, s)

Example 43: N1-(1H-5-Indazolyl)-3-(5-nitro-2-furyl)propeneamide

[0278] 5-Aminoindazole (175 mg, 1.32 mmol, 1.0 eq), WSC · HCl (303 mg, 1.58 mmol, 1.2 eq), and HOBr·H₂O (213 mg, 1.58 mmol, 1.2 eq) were added to a solution of 3-(5-nitro-2-furyl)acrylic acid (240 mg, 1.32 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0279] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (180 mg, 46.1%).

[0280] Palladium hydroxide (one small spatula) was added to a solution of the crystal (30 mg, 0.1 mmol) in DMF, and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hr.

[0281] After the completion of the reaction, the reaction solution was filtered through Celite, and washing with ethyl acetate was carried out. Water was poured into the filtrate, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was then dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give the title compound as a crystal (7 mg, 26.7%).

MS m/z: 300

¹H-NMR δ: 2.77 (2H, t, J = 7.44 Hz), 3.10 (2H, t, J = 7.32 Hz), 6.64 (1H, d, J = 3.66 Hz), 7.39 (1H, d, J = 9.03 Hz), 7.47 (1H, d, J = 8.78 Hz), 7.64 (1H, d, J = 3.66 Hz), 8.00 (1H, s), 8.10 (1H, s), 10.03 (1H, s), 12.95 (1H, s)

Example 44: N1-(1H-5-Indazolyl)-2-(3,4-dihydroxyphenyl)-acetamide

[0282] 5-Aminoindazole (158 mg, 1.19 mmol, 1.0 eq), WSC · HCl (274 mg, 1.43 mmol, 1.2 eq), and HOBr·H₂O (193

mg, 1.43 mmol, 1.2 eq) were added to a solution of 3,4-dihydroxyacetic acid (200 mg, 1.19 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0283] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was then dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (33 mg, 9.8%).

MS m/z: 283

¹H-NMR δ: 3.43 (2H, s), 6.58 (1H, dd, J = 2.20, 8.05 Hz), 6.66 (1H, d, J = 8.05 Hz), 6.76 (1H, d, J = 2.20 Hz), 7.41 (1H, dd, J = 1.46, 9.03 Hz), 7.44 (1H, d, J = 8.78 Hz), 7.99 (1H, s), 8.11 (1H, s), 8.76 (2H, s), 10.01 (1H, s), 12.94 (1H, s)

Example 45: N1-(1H-5-Indazolyl)-2-(1,3-benzodioxol-5-yl)acetamide

[0284] 5-Aminoindazole (158 mg, 1.19 mmol, 1.0 eq), WSC · HCl (274 mg, 1.43 mmol, 1.2 eq), and HOBr · H₂O (193 mg, 1.43 mmol, 1.2 eq) were added to a solution of 3,4-methylenedioxypyrenylacetic acid (214 mg, 1.19 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0285] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was then dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (166 mg, 47.4%).

MS m/z: 295

¹H-NMR δ: 3.55 (2H, s), 5.98 (2H, s), 6.80 (1H, dd, J = 1.34, 7.93 Hz), 6.86 (1H, d, J = 8.05 Hz), 6.92 (1H, d, J = 1.46), 7.41 (1H, dd, J = 1.71, 8.78 Hz), 7.47 (1H, d, J = 9.03 Hz), 7.99 (1H, s), 8.09 (1H, s), 10.07 (1H, s), 12.95 (1H, s)

Example 46: N1-(1H-5-Indazolyl)-3-(3,4-dihydroxyphenyl)-propeneamide

[0286] 5-Aminoindazole (146 mg, 1.10 mmol, 1.0 eq), WSC · HCl (253 mg, 1.32 mmol, 1.2 eq), and HOBr · H₂O (178 mg, 1.32 mmol, 1.2 eq) were added to a solution of 3,4-dihydroxycinnamic acid (200 mg, 1.10 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0287] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (79 mg, 24.2%).

MS m/z: 297

¹H-NMR δ: 2.53 (2H, t, J = 8.29 Hz), 2.75 (2H, t, J = 7.56 Hz), 6.48 (1H, dd, J = 2.20, 8.05 Hz), 6.62 (1H, d, J = 8.05 Hz), 6.63 (1H, s), 7.38 (1H, dd, J = 1.71, 9.03 Hz), 7.45 (1H, d, J = 8.78 Hz), 7.99 (1H, s), 8.11 (1H, s), 8.61 (1H, s), 8.70 (1H, s), 9.84 (1H, s), 12.93 (1H, s)

Example 47: N1-(1H-5-Indazolyl)-3-(4-hydroxyphenyl)-propaneamide

[0288] 5-Aminoindazole (119 mg, 0.89 mmol, 1.0 eq), WSC · HCl (205 mg, 1.07 mmol, 1.2 eq), and HOBr · H₂O (145 mg, 1.07 mmol, 1.2 eq) were added to a solution of 3-(4-hydroxyphenyl)propionic acid (148 mg, 0.89 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0289] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was then dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (95 mg, 38.0%).

MS m/z: 281

¹H-NMR δ: 2.55 (2H, t, J = 7.68 Hz), 2.81 (2H, t, J = 7.56 Hz), 6.66 (2H, d, J = 8.29 Hz), 7.04 (2H, d, J = 8.54 Hz), 7.38 (1H, dd, J = 1.71, 8.78 Hz), 7.45 (1H, d, J = 9.03 Hz), 7.99 (1H, s), 8.10 (1H, s), 9.84 (1H, s), 12.93 (1H, s)

Example 48: N1-(1H-5-Indazolyl)-2-(3-nitrophenyl)-acetamide

[0290] 5-Aminoindazole (147 mg, 1.10 mmol, 1.0 eq), WSC · HCl (254 mg, 1.32 mmol, 1.2 eq), and HOBr · H₂O (179 mg, 1.32 mmol, 1.2 eq) were added to a solution of 3-nitrophenylacetic acid (200 mg, 1.10 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0291] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was then dried over sodium

sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (172 mg, 52.6%).

MS m/z: 296

⁵ ¹H-NMR δ: 3.86 (2H, s), 7.43 (1H, dd, J = 1.71, 8.78 Hz), 7.49 (1H, d, J = 9.03 Hz), 7.65 (1H, t, J = 7.93 Hz), 7.82 (1H, d, J = 7.56 Hz), 8.00 (1H, s), 8.12 (1H, s), 8.14 (1H, dd, J = 2.44, 8.29 Hz), 8.26 (1H, s), 10.28 (1H, s), 12.98 (1H, s)

Example 49: N1-(1H-5-Indazolyl)-2-(4-nitrophenyl)-acetamide

¹⁰ [0292] 5-Aminoindazole (147 mg, 1.10 mmol, 1.0 eq), WSC · HCl (254 mg, 1.32 mmol, 1.2 eq), and HOBr · H₂O (179 mg, 1.32 mmol, 1.2 eq) were added to a solution of 4-nitrophenylacetic acid (200 mg, 1.10 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

¹⁵ [0293] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (110 mg, 33.7%).

MS m/z: 296

²⁰ ¹H-NMR δ: 3.85 (2H, s), 7.42 (1H, dd, J = 1.71, 8.78 Hz), 7.48 (1H, d, J = 9.03 Hz), 7.64 (2H, d, J = 8.78 Hz), 8.00 (1H, s), 8.10 (1H, s), 8.21 (2H, d, J = 8.78 Hz), 10.28 (1H, s), 12.98 (1H, s)

Example 50: N1-(1H-5-Indazolyl)-2-(4-hydroxyanilino)-acetamide

²⁵ [0294] 5-Aminoindazole (159 mg, 1.20 mmol, 1.0 eq), WSC · HCl (276 mg, 1.44 mmol, 1.2 eq), and HOBr · H₂O (194 mg, 1.44 mmol, 1.2 eq) were added to a solution of N-(4-hydroxyphenyl)glycine (200 mg, 1.20 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0295] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (46 mg, 13.6%).

MS m/z: 283

³⁰ ¹H-NMR δ: 3.76 (2H, d, J = 5.85 Hz), 5.41 (1H, t, J = 5.85 Hz), 6.48 (2H, d, J = 8.78 Hz), 6.57 (2H, d, J = 8.78 Hz), 7.43 (1H, dd, J = 1.46, 9.03 Hz), 7.47 (1H, d, J = 9.03 Hz), 8.00 (1H, s), 8.10 (1H, s), 8.48 (1H, s), 9.84 (1H, s), 12.95 (1H, s)

Example 51: N1-(1H-5-Indazolyl)-2-(4-hydroxyphenoxy)-acetamide

[0296] 5-Aminoindazole (158 mg, 1.19 mmol, 1.0 eq), WSC · HCl (274 mg, 1.43 mmol, 1.2 eq), and HOBr · H₂O (193 mg, 1.43 mmol, 1.2 eq) were added to a solution of 4-hydroxyphenoxyacetic acid (200 mg, 1.19 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0297] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (229 mg, 68.0%).

MS m/z: 283

⁴⁵ ¹H-NMR δ: 4.57 (2H, s), 6.70 (2H, d, J = 9.03 Hz), 6.86 (2H, d, J = 9.03 Hz), 7.49 (2H, s), 8.03 (1H, s), 8.13 (1H, s), 9.00 (1H, s), 9.98 (1H, s), 12.99 (1H, s)

Example 52: N1-(1H-5-Indazolyl)-3-(1,3-benzodioxol-5-yl)propaneamide

[0298] 5-Aminoindazole (137 mg, 1.03 mmol, 1.0 eq), WSC · HCl (237 mg, 1.24 mmol, 1.2 eq), and HOBr · H₂O (167 mg, 1.24 mmol, 1.2 eq) were added to a solution of 3-(3,4-methylenedioxyphenyl)propionic acid (200 mg, 1.03 mmol) in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0299] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (98 mg, 30.8%).

MS m/z: 309

⁵⁵ ¹H-NMR δ: 2.58 (2H, t, J = 7.68 Hz), 2.85 (2H, t, J = 7.68 Hz), 5.95 (2H, s), 6071 (1H, dd, J = 1.59, 7.93 Hz), 6.81 (1H, d, J = 8.05 Hz), 6.84 (1H, d, J = 1.46 Hz), 7.38 (1H, dd, J = 1.71, 9.03), 7.46 (1H, d, J = 9.03 Hz), 8.00 (1H, s), 8.11 (1H, s), 9.86 (1H, s), 12.94 (1H, s)

Example 53: N-(2,4-Dichlorobenzyl)-N'-(4-pyridyl)urea

[0300] Diphenylphosphoryl azide (161 mg, 0.59 mmol, 1.2 eq) and triethylamine (59 mg, 0.59 mmol, 1.2 eq) were added to a solution of 2,4-dichlorophenylacetic acid (100 mg, 0.49 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0301] Thereafter, 4-aminopyridine (46 mg, 0.49 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0302] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (43 mg, 29.9%).

MS m/z: 295

¹H-NMR δ: 4.35 (2H, d, J = 5.85 Hz), 6.94 (1H, t, J = 5.98 Hz), 7.37 (2H, dd, J = 1.59, 4.76 Hz), 7.39 (1H, d, J = 8.42 Hz), 7.44 (1H, dd, J = 2.07, 8.42 Hz), 7.61 (1H, d, J = 2.20 Hz), 8.29 (2H, dd, J = 1.46, 4.88 Hz), 9.17 (1H, s)

Example 54: N-(2-Chloro-4-nitrobenzyl)-N'-(4-pyridyl)-urea

[0303] Toluene (1 ml) and a minor amount of DMF were added to 4-aminopyridine (50 mg, 0.53 mmol), and the mixture was heated. Thereafter, 2-chloro-4-nitrophenyl isocyanate (105 mg, 0.53 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 150 min.

[0304] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (72 mg, 46.4%).

MS m/z: 292

¹H-NMR δ: 7.57 (1H, s), 8.23 (2H, dd, J = 2.68, 9.27 Hz), 8.36 (2H, d, J = 2.44 Hz), 8.53 (2H, d, J = 9.27 Hz), 8.96 (1H, s), 10.09 (1H, s)

Example 55: N'-(4-Pyridyl)-N-(2,3,6-trichlorobenzyl)urea

[0305] Diphenylphosphoryl azide (182 mg, 0.66 mmol, 1.2 eq) and triethylamine (67 mg, 0.66 mmol, 1.2 eq) were added to a solution of 2,3,6-trichlorophenylacetic acid (132 mg, 0.55 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0306] Thereafter, 4-aminopyridine (52 mg, 0.55 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0307] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (153 mg, 84.0%).

MS m/z: 330, 332

¹H-NMR δ: 4.74 (2H, s), 7.22 (2H, dd, J = 2.68, 8.54 Hz), 7.38 (2H, dd, J = 1.46, 5.37 Hz), 8.14 (2H, d, J = 5.61 Hz)

Example 56: N-(2-Chloro-6-fluorobenzyl)-N'-(4-pyridyl)-urea

[0308] Diphenylphosphoryl azide (182 mg, 0.66 mmol, 1.2 eq) and triethylamine (67 mg, 0.66 mmol, 1.2 eq) were added to a solution of 2-chloro-6-fluorophenylacetic acid (104 mg, 0.55 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0309] Thereafter, 4-aminopyridine (52 mg, 0.55 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0310] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (96 mg, 62.3%).

MS m/z: 280

¹H-NMR δ: 4.60 (2H, d, J = 1.46 Hz), 6.99 (1H, dt, J = 7.07, 9.51 Hz), 7.15 - 7.22 (2H, m), 7.31 (2H, dd, J = 1.46, 4.88 Hz), 8.24 (2H, dd, J = 1.46, 4.88 Hz)

Example 57: N-(2-Bromo-4,6-difluorobenzyl)-N'-(4-pyridyl)urea

[0311] Toluene (1 ml) and a minor amount of DMF were added to 4-aminopyridine (50 mg, 0.53 mmol), and the mixture was heated. Thereafter, 2-bromo-4,6-difluorophenyl isocyanate (124 mg, 0.53 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 120 min.

[0312] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (107 mg, 61.5%).

MS m/z: 327, 329

⁵ ¹H-NMR δ: 7.43 (2H, dd, J = 1.46, 4.88 Hz), 7.48 (1H, dd, J = 2.80, 9.88), 7.59 (1H, dd, J = 1.71, 8.29 Hz), 8.27 (1H, s), 8.35 (2H, dd, J = 1.46, 4.88 Hz), 9.46 (1H, s)

Example 58: N-[4-Fluoro-6-(trifluoromethyl)phenyl]-N'-(4-pyridyl)urea

[0313] Toluene (1 ml) and a minor amount of DMF were added to 4-aminopyridine (50 mg, 0.53 mmol), and the mixture was heated. Thereafter, 2-fluoro-6-(trifluoromethyl)phenyl isocyanate (109 mg, 0.53 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 120 min.

[0314] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (69 mg, 43.7%).

MS m/z: 299

¹⁵ ¹H-NMR δ: 7.45 (2H, dd, J = 1.59, 4.76 Hz), 7.48 - 7.64 (3H, m), 8.34 (1H, s), 8.39 (2H, dd, J = 1.59, 4.76 Hz), 9.28 (1H, s)

Example 59: N-[4-Fluoro-2-(trifluoromethyl)phenyl]-N'-(4-pyridyl)urea

²⁰ [0315] Toluene (1 ml) and a minor amount of DMF were added to 4-aminopyridine (50 mg, 0.53 mmol), and the mixture was heated. Thereafter, 4-fluoro-2-(trifluoromethyl)phenyl isocyanate (109 mg, 0.53 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 120 min.

[0316] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (72 mg, 45.3%).

MS m/z: 299

²⁵ ¹H-NMR δ: 7.43 (2H, dd, J = 1.59, 4.76 Hz), 7.56 (1H, dt, J = 3.03, 8.54 Hz), 7.62 (1H, dd, J = 2.93, 9.03 Hz), 7.86 (1H, dd, J = 5.12, 8.78 Hz), 8.28 (1H, s), 8.37 (2H, dd, J = 1.46, 4.88 Hz), 9.63 (1H, s)

Example 60: N-(4-Bromo-2-fluorophenyl)-N'-(4-pyridyl)-urea

[0317] Toluene (1 ml) and a minor amount of DMF were added to 4-aminopyridine (50 mg, 0.53 mmol), and the mixture was heated. Thereafter, 4-bromo-2-fluorophenyl isocyanate (115 mg, 0.53 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 120 min.

[0318] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (13 mg, 7.9%).

MS m/z: 309, 311

³⁰ ¹H-NMR δ: 7.37 (1H, dt, J = 1.34, 8.66 Hz), 7.42 (2H, dt, J = 1.59, 4.76 Hz), 7.58 (1H, dd, J = 2.32, 10.86 Hz), 8.09 (1H, dt, J = 3.17, 8.78 Hz), 8.37 (2H, d, J = 6.34 Hz), 8.80 (1H, s), 9.45 (1H, s)

Example 61: N-(2,6-Difluorobenzyl)-N'-(4-pyridyl)urea

[0319] Diphenylphosphoryl azide (191 mg, 0.69 mmol, 1.2 eq) and triethylamine (70 mg, 0.69 mmol, 1.2 eq) were added to a solution of 2,6-difluorophenylacetic acid (100 mg, 0.58 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0320] Thereafter, 4-aminopyridine (55 mg, 0.58 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0321] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (87 mg, 57.0%).

MS m/z: 263

⁴⁵ ¹H-NMR δ: 4.39 (2H, d, J = 5.37 Hz), 6.84 (1H, t, J = 5.73 Hz), 7.10 (2H, t, J = 8.17 Hz), 7.33 (2H, dd, J = 1.59, 4.76 Hz), 7.40 (1H, dt, J = 1.59, 8.29 Hz), 8.27 (2H, dd, J = 1.59, 4.76 Hz), 8.87 (1H, s)

Example 62: N-Mesitylmethyl-N'-(4-pyridyl)urea

[0322] Diphenylphosphoryl azide (191 mg, 0.69 mmol, 1.2 eq) and triethylamine (70 mg, 0.69 mmol, 1.2 eq) were added to a solution of 2,4,6-trimethylphenylacetic acid (103 mg, 0.58 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0323] Thereafter, 4-aminopyridine (55 mg, 0.58 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0324] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (88 mg, 56.8%).

MS m/z: 270

¹H-NMR δ: 2.25 (3H, s), 2.33 (6H, s), 4.39 (2H, s), 6.85 (2H, s), 7.31 (2H, dd, J = 1.71, 4.88 Hz), 8.19 (2H, dd, J = 1.71, 4.88 Hz)

Example 63: N-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-N'-(4-pyridyl)urea

[0325] Diphenylphosphoryl azide (174 mg, 0.63 mmol, 1.2 eq) and triethylamine (64 mg, 0.63 mmol, 1.2 eq) were added to a solution of 2,6-dichloro-4-trifluoromethylbenzoic acid (137 mg, 0.53 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0326] Thereafter, 4-aminopyridine (50 mg, 0.53 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0327] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (102 mg, 54.9%).

MS m/z: 349

¹H-NMR δ: 4.63 (2H, d, J = 5.37 Hz), 6.87 (1H, t, J = 5.49 Hz), 7.34 (2H, dd, J = 1.46, 4.88 Hz), 7.94 (2H, s), 8.28 (2H, dd, J = 1.34, 5.00 Hz), 8.90 (1H, s)

Example 64: N-[2-Fluoro-6-(trifluoromethyl)benzyl]-N'-(4-pyridyl)urea

[0328] Diphenylphosphoryl azide (174 mg, 0.63 mmol, 1.2 eq) and triethylamine (64 mg, 0.63 mmol, 1.2 eq) were added to a solution of 2-fluoro-6-trifluoromethylacetic acid (112 mg, 0.53 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0329] Thereafter, 4-aminopyridine (50 mg, 0.53 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0330] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (102 mg, 54.9%).

MS m/z: 313

¹H-NMR δ: 4.51 (2H, d, J = 4.88 Hz), 6.69 (1H, t, J = 5.00 Hz), 7.34 (2H, dd, J = 1.46, 4.88 Hz), 7.59 - 7.64 (3H, m), 8.28 (2H, s), 8.28 (2H, d, J = 6.34 Hz), 8.82 (1H, s)

Example 65: 4-{{(2,6-Dichloroanilino)carbonyl}amino}-benzamide

[0331] Toluene (1 ml) and a minor amount of DMF were added to 4-aminobenzamide (113 mg, 0.73 mmol), and the mixture was heated. Thereafter, 2,6-dichlorophenyl isocyanate (138 mg, 0.73 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 150 min.

[0332] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (205 mg, 86.2%).

MS m/z: 323

¹H-NMR δ: 7.16 (1H, s), 7.33 (1H, t, J = 8.17 Hz), 7.51 (2H, d, J = 8.24 Hz), 7.54 (2H, d, J = 8.29 Hz), 7.80 (2H, d, J = 8.54 Hz), 8.30 (1H, s), 9.21 (1H, s)

Example 66: N-(1H-3-Indolyl)-N'-(4-pyridyl)urea

[0333] Diphenylphosphoryl azide (205 mg, 0.75 mmol, 1.2 eq) and triethylamine (75 mg, 0.75 mmol, 1.2 eq) were added to a solution of 3-indolecarboxylic acid (100 mg, 0.62 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0334] Thereafter, 4-aminopyridine (58 mg, 0.62 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0335] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (54 mg, 34.5%).

MS m/z: 326

¹H-NMR δ: 7.02 (1H, t, J = 7.44 Hz), 7.11 (1H, t, J = 7.56 Hz), 7.35 (1H, d, J = 8.05 Hz), 7.46 (2H, dd, J = 1.59, 4.76 Hz), 7.51 (1H, d, J = 5.12 Hz), 7.52 (1H, s), 8.43 (2H, d, J = 6.34 Hz), 8.66 (1H, s), 9.02 (1H, s), 10.79 (1H, s)

Example 67: N-(2,6-Dichlorophenyl)-N'-(1,3-dioxo-2,3-dihydro-1H-isoindolyl)urea

[0336] Toluene (1 ml) and a minor amount of DMF were added to 4-aminophthalimide (86 mg, 0.53 mmol), and the mixture was heated. Thereafter, 2,6-dichlorophenyl isocyanate (100 mg, 0.53 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 150 min.

[0337] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (150 mg, 80.6%).

MS m/z: 349

¹H-NMR δ: 7.35 (1H, dd, J = 7.81, 8.03 Hz), 7.60 (2H, d, J = 8.05 Hz), 7.72 (2H, d, J = 1.22 Hz), 8.04 (1H, d, J = 1.22 Hz), 8.50 (1H, s), 9.69 (1H, s), 11.13 (1H, s)

Example 68: N1-(2,6-Dichlorobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0338] Diphenylphosphoryl azide (161 mg, 0.59 mmol, 1.2 eq) and triethylamine (59 mg, 0.59 mmol, 1.2 eq) were added to a solution of 2,6-dichlorophenylacetic acid (100 mg, 0.49 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0339] Thereafter, 4-aminophthalimide (79 mg, 0.49 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0340] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (120 mg, 67.6%).

MS m/z: 364

¹H-NMR δ: 4.60 (2H, d, J = 5.37 Hz), 6.78 (1H, t, J = 5.37 Hz), 7.39 (1H, d, J = 7.30 Hz), 7.51 (2H, d, J = 7.81 Hz), 7.55 (1H, dd, J = 1.95, 8.29 Hz), 7.67 (1H, d, J = 8.29 Hz), 8.01 (1H, d, J = 1.95 Hz), 9.14 (1H, s), 11.09 (1H, s)

Example 69: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(1H-3-indolyl)urea

[0341] Diphenylphosphoryl azide (161 mg, 0.59 mmol, 1.2 eq) and triethylamine (59 mg, 0.59 mmol, 1.2 eq) were added to a solution of 3-indoleacetic acid (79 mg, 0.49 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0342] Thereafter, 4-aminophthalimide (79 mg, 0.49 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0343] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by a preparative TLC [chloroform-acetone] to give the title compound as a crystal (30 mg, 19.1%).

MS m/z: 320

¹H-NMR δ: 7.02 (1H, t, J = 7.56 Hz), 7.11 (1H, t, J = 7.56 Hz), 7.16 (1H, d, J = 7.81 Hz), 7.35 (1H, d, J = 8.05 Hz), 7.54 (2H, d, J = 7.81 Hz), 7.67 (1H, dd, J = 1.83, 8.17 Hz), 7.72 (1H, d, J = 8.05 Hz), 8.12 (1H, d, J = 1.22), 9.35 (1H, s), 10.81 (1H, s), 11.11 (1H, s)

Example 70: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(1H-5-indolyl)urea

[0344] Diphenylphosphoryl azide (161 mg, 0.59 mmol, 1.2 eq) and triethylamine (59 mg, 0.59 mmol, 1.2 eq) were added to a solution of 5-indoleacetic acid (79 mg, 0.49 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0345] Thereafter, 4-aminophthalimide (79 mg, 0.49 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0346] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by a preparative TLC [chloroform-acetone] to give the title compound as a crystal (50 mg, 31.9%).

MS m/z: 320

¹H-NMR δ: 6.36 - 6.39 (1H, m), 7.29 - 7.34 (3H, m), 7.64 - 7.75 (3H, m), 8.07 (1H, d, J = 1.46 Hz), 8.64 (1H, s), 9.29 (1H, s), 10.98 (1H, s), 11.11 (1H, s)

Example 71: N-(2-Nitrobenzyl)-N'-(4-pyridyl)urea

[0347] Toluene (1 ml) and a minor amount of DMF were added to 4-aminopyridine (80 mg, 0.85 mmol), and the mixture was heated. Thereafter, 2-nitrophenyl isocyanate (139 mg, 0.85 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 150 min.

[0348] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (170 mg, 77.8%).

MS m/z: 258

¹H-NMR δ: 7.26 (1H, dt, J = 1.22, 7.08 Hz), 7.46 (2H, dd, J = 1.59, 4.76 Hz), 7.73 (1H, dt, J = 1.59, 7.20 Hz), 8.10 (1H, dd, J = 1.59, 8.42 Hz), 8.24 (1H, dd, J = 1.34, 8.42 Hz), 8.40 (2H, dd, J = 1.59, 4.76 Hz), 9.69 (1H, s), 10.16 (1H, s)

Example 72: N1-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-phenylurea

[0349] Toluene (1 ml) and a minor amount of DMF were added to 4-aminophthalimide (80 mg, 0.50 mmol), and the mixture was heated. Thereafter, phenyl isocyanate (59 mg, 0.50 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 150 min.

[0350] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (95 mg, 68.3%).

MS m/z: 281

¹H-NMR δ: 7.01 (1H, t, J = 7.32 Hz), 7.31 (2H, t, J = 7.93 Hz), 7.48 (2H, dd, J = 0.98, 8.54 Hz), 7.67 (1H, dd, J = 1.83, 8.17 Hz), 7.73 (1H, d, J = 8.29 Hz), 8.05 (1H, d, J = 1.46 Hz), 8.89 (1H, s), 9.36 (1H, s), 11.14 (1H, s)

Example 73: N-Benzyl-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0351] Toluene (1 ml) and a minor amount of DMF were added to 4-aminophthalimide (80 mg, 0.50 mmol), and the mixture was heated. Thereafter, benzyl isocyanate (66 mg, 0.50 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 150 min.

[0352] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (96 mg, 65.7%).

MS m/z: 295

¹H-NMR δ: 4.33 (2H, d, J = 4.39 Hz), 6.90 (1H, t, J = 5.98 Hz), 7.22 - 7.35 (5H, m), 7.61 (1H, dd, J = 1.83, 8.17 Hz), 7.67 (1H, d, J = 8.29 Hz), 8.02 (1H, dd, J = 0.49, 1.95 Hz), 9.30 (1H, s), 11.08 (1H, s)

Example 74: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-propylurea

[0353] Toluene (1 ml) and a minor amount of DMF were added to 4-aminophthalimide (80 mg, 0.50 mmol), and the mixture was heated. Thereafter, n-propyl isocyanate (42 mg, 0.50 mmol, 1.0 eq) was added thereto, and the mixture was stirred at 110°C for 150 min.

[0354] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by a preparative TLC [chloroform-acetone] to give the title compound as a crystal (35 mg, 28.9%).

MS m/z: 247

¹H-NMR δ: 0.88 (3H, t, J = 7.44 Hz), 1.41 - 1.51 (2H, m), 3.07 (2H, q, J = 5.60 Hz), 6.40 (1H, t, J = 5.60 Hz), 7.58 (1H, dd, J = 2.07, 8.17 Hz), 7.66 (1H, d, J = 8.29 Hz), 8.00 (1H, d, J = 1.71 Hz), 9.14 (1H, s), 11.06 (1H, s)

Example 75: N-Cyclohexylmethyl-N'-(4-pyridyl)urea

[0355] Diphenylphosphoryl azide (232 mg, 0.85 mmol, 1.2 eq) and triethylamine (85 mg, 0.85 mmol, 1.2 eq) were added to a solution of cyclohexylacetic acid (100 mg, 0.70 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0356] Thereafter, 4-aminopyridine (66 mg, 0.70 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 150 min.

[0357] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (13 mg, 7.9%).

MS m/z: 234

¹H-NMR δ: 0.84 - 0.96 (2H, m), 1.09 - 1.25 (3H, m), 1.33 - 1.45 (1H, m), 1.58 - 1.72 (5H, m), 2.94 (2H, t, J = 6.22 Hz), 6.37 (1H, t, J = 5.73 Hz), 7.34 (2H, dd, J = 1.46, 4.88 Hz), 8.26 (2H, dd, J = 1.59, 4.76 Hz), 8.80 (1H, s)

Example 76: N-Cyclohexylmethyl-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0358] Diphenylphosphoryl azide (232 mg, 0.85 mmol, 1.2 eq) and triethylamine (85 mg, 0.85 mmol, 1.2 eq) were added to a solution of cyclohexylacetic acid (100 mg, 0.70 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0359] Thereafter, 4-aminophthalimide (114 mg, 0.70 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 150 min.

[0360] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by a preparative TLC [chloroform-acetone] to give the title compound as a crystal (46 mg, 21.7%).

MS m/z: 301

¹H-NMR δ: 0.85 - 0.96 (2H, m), 1.07 - 1.26 (3H, m), 1.35 - 1.47 (1H, m), 1.58 - 1.73 (5H, m), 2.97 (2H, t, J = 6.22 Hz), 6.42 (1H, t, J = 5.73 Hz), 7.56 (1H, dd, J = 1.95, 8.29 Hz), 7.66 (1H, d, J = 8.30 Hz), 8.01 (1H, d, J = 1.71 Hz), 9.11 (1H, s), 11.06 (1H, s)

Example 77: N-(4-Pyridyl)-N'-(2,4,6-trifluorobenzyl)urea

[0361] Diphenylphosphoryl azide (174 mg, 0.63 mmol, 1.2 eq) and triethylamine (64 mg, 0.63 mmol, 1.2 eq) were added to a solution of 2,4,6-trifluorophenylacetic acid (100 mg, 0.53 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0362] Thereafter, 4-aminopyridine (50 mg, 0.53 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0363] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (80 mg, 56.5%).

MS m/z: 269

¹H-NMR δ: 4.34 (2H, d, J = 5.61 Hz), 6.86 (1H, t, J = 5.61 Hz), 7.19 (2H, t, J = 8.78 Hz), 7.33 (2H, dd, J = 1.59, 4.88 Hz), 8.28 (2H, dd, J = 1.58, 4.88 Hz), 8.88 (1H, s)

Example 78: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(3-nitrophenyl)urea

[0364] Toluene (1 ml) and a minor amount of DMF were added to 4-aminopyridine (80 mg, 0.85 mmol), and the mixture was heated. Thereafter, 3-nitrophenyl isocyanate (81 mg, 0.85 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 180 min.

[0365] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (150 mg, 93%).

MS m/z: 326

¹H-NMR δ: 7.60 (1H, t, J = 8.17 Hz), 7.71 - 7.80 (3H, m), 7.85 - 7.89 (1H, m), 8.04 - 8.06 (1H, m), 8.56 (1H, t, J = 0.85 Hz), 9.46 (1H, s), 9.55 (1H, s), 11.17 (1H, s)

Example 79: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(4-aminophenyl)urea

[0366] A minor amount of palladium hydroxide was added to a solution of the compound (84 mg, 0.26 mmol), prepared

in Example 78, in DMF, and the mixture was stirred under a hydrogen atmosphere at room temperature for one hr. [0367] After the completion of the reaction, the reaction solution was filtered through Celite, and washing with ethyl acetate was carried out. The filtrate was washed with water and saturated brine and was then dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give the title compound as a crystal (44 mg, 57.9%).

MS m/z: 296

¹H-NMR δ: 5.05 (2H, s), 6.23 (1H, dd, J = 1.71, 7.81 Hz), 6.58 (1H, dd, J = 1.46, 7.81 Hz), 6.78 (1H, t, J = 2.07 Hz), 6.92 (1H, t, J = 7.93 Hz), 7.63 (1H, dd, J = 1.83, 8.17 Hz), 7.71 (1H, d, J = 8.05 Hz), 8.05 (1H, d, J = 1.95 Hz), 8.58 (1H, s), 9.24 (1H, s), 11.12 (1H, s)

Example 80: N-(2,6-Dichlorobenzyl)-N'-(4-pyridyl)urea

[0368] Diphenylphosphoryl azide (242 mg, 0.88 mmol, 1.2 eq) and triethylamine (89 mg, 0.88 mmol, 1.2 eq) were added to a solution of 2,6-dichlorophenylacetic acid (150 mg, 0.73 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0369] Thereafter, 4-aminopyridine (69 mg, 0.73 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0370] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (76 mg, 32.4%).

MS m/z: 296

¹H-NMR δ: 6.08 (2H, d, J = 5.37 Hz), 6.73 (1H, t, J = 5.37 Hz), 7.34 (2H, dd, J = 1.58, 4.88 Hz), 7.38 (1H, dd, J = 1.22, 7.32 Hz), 7.51 (2H, d, J = 7.81 Hz), 8.28 (2H, dd, J = 1.71, 4.88 Hz), 8.84 (1H, s)

Example 81: N-(6-Chloro-1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(2,6-dichlorobenzyl)urea

[0371] Diphenylphosphoryl azide (242 mg, 0.88 mmol, 1.2 eq) and triethylamine (89 mg, 0.88 mmol, 1.2 eq) were added to a solution of 2,6-dichlorophenylacetic acid (150 mg, 0.73 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0372] Thereafter, 4-amino-5-chlorophthalimide (130 mg, 0.66 mmol, 0.9 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0373] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate. The resultant crystal was purified by a preparative TLC [chloroform/methanol] to give the title compound as a crystal (11 mg, 3.8%).

MS m/z: 397, 399

¹H-NMR δ: 4.60 - 4.64 (2H, m), 7.36 - 7.46 (3H, m), 7.54 (2H, d, J = 7.81 Hz), 7.87 (1H, s), 8.71 (1H, s), 11.28 (1H, s)

Example 82: N-(2-Chlorobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0374] Diphenylphosphoryl azide (165 mg, 0.60 mmol, 1.2 eq) and triethylamine (61 mg, 0.60 mmol, 1.2 eq) were added to a solution of 2-chlorophenylacetic acid (85 mg, 0.50 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0375] Thereafter, 4-aminophthalimide (81 mg, 0.50 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0376] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (37 mg, 22.6%).

MS m/z: 329

¹H-NMR δ: 4.40 (2H, d, J = 5.61 Hz), 6.94 (1H, t, J = 5.98 Hz), 7.28 - 7.38 (2H, m), 7.41 (1H, dd, J = 1.71, 7.56 Hz), 7.46 (1H, dd, J = 1.71, 7.56 Hz), 7.61 (1H, dd, J = 1.83, 8.17 Hz), 7.68 (1H, d, J = 8.54 Hz), 8.01 (1H, d, J = 1.46 Hz), 9.42 (1H, s), 11.08 (1H, s)

Example 83: N-(2-Chloro-6-fluorobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-6-isoindolyl)urea

[0377] Diphenylphosphoryl azide (165 mg, 0.60 mmol, 1.2 eq) and triethylamine (61 mg, 0.60 mmol, 1.2 eq) were added to a solution of 2-chloro-6-fluorophenylacetic acid (94 mg, 0.50 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0378] Thereafter, 4-aminophthalimide (81 mg, 0.50 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0379] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal

was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (58 mg, 33.5%).

MS m/z: 346, 348

¹H-NMR δ: 4.49 (2H, d, J = 4.15 Hz), 6.84 (1H, t, J = 5.49 Hz), 7.25 (1H, dt, J = 1.59, 7.81 Hz), 7.32 - 7.43 (2H, m), 7.55 (1H, dd, J = 1.83, 8.17 Hz), 7.66 (1H, d, J = 8.29 Hz), 7.99 (1H, d, J = 1.95 Hz), 9.15 (1H, s), 11.08 (1H, s)

5

Example 84: N-Benzyl-N'-(1H-5-indazolyl)urea

[0380] Toluene (1 ml) and a minor amount of DMF were added to 5-aminoindazole (67 mg, 0.50 mmol), and the mixture was heated. Thereafter, benzyl isocyanate (66 mg, 0.50 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 180 min.

[0381] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0382] Methanol was added to the residue, followed by filtration to give the title compound as a crystal (21 mg, 15.9%).

MS m/z: 266

¹H-NMR δ: 4.31 (2H, d, J = 5.85 Hz), 6.53 (1H, t, J = 5.85 Hz), 7.21 - 7.28 (2H, m), 7.29 - 7.36 (3H, m), 7.41 (1H, d, J = 8.78 Hz), 7.85 (1H, s), 7.93 (1H, s), 8.46 (1H, s), 12.84 (1H, s)

Example 85: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(1-naphthylmethyl)urea

[0383] Diphenylphosphoryl azide (204 mg, 0.74 mmol, 1.2 eq) and triethylamine (75 mg, 0.74 mmol, 1.2 eq) were added to a solution of 1-naphthylacetic acid (115 mg, 0.62 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0384] Thereafter, 4-aminophthalimide (100 mg, 0.62 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0385] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (91 mg, 42.7%).

MS m/z: 345

¹H-NMR δ: 4.80 (2H, d, J = 4.39 Hz), 6.95 (1H, t, J = 5.73 Hz), 7.47 - 7.62 (5H, m), 7.67 (1H, d, J = 8.29 Hz), 7.87 (1H, dd, J = 1.95, 7.32 Hz), 7.96 (1H, dd, J = 1.46, 8.05 Hz), 8.04 (1H, d, J = 1.22 Hz), 8.14 (1H, d, J = 8.54 Hz), 9.27 (1H, s), 11.08 (1H, s)

Example 86: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(2-nitrobenzyl)urea

[0386] Diphenylphosphoryl azide (165 mg, 0.60 mmol, 1.2 eq) and triethylamine (61 mg, 0.60 mmol, 1.2 eq) were added to a solution of 2-nitrophenylacetic acid (90 mg, 0.50 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0387] Thereafter, 4-aminophthalimide (81 mg, 0.50 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2 hr.

[0388] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration, was washed with ethyl acetate, and was further washed with a chloroform/methanol solution to give the title compound as a crystal (11 mg, 6.5%).

MS m/z: 340

¹H-NMR δ: 4.61 (2H, d, J = 5.37 Hz), 7.00 (1H, t, J = 5.73 Hz), 7.53 - 7.70 (4H, m), 7.76 (1H, t, J = 7.44 Hz), 8.00 (1H, s), 8.06 (1H, d, J = 7.44 Hz), 9.48 (1H, s), 11.09 (1H, s)

Example 87: N'-(2-Aminobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0389] Palladium hydroxide (one small spatula) was added to a solution of the crystal (100 mg, 0.29 mmol) of the compound prepared in Example 86 (mixed with 4-aminophthalimide) in DMF, and the mixture was stirred under a hydrogen atmosphere at room temperature for 60 min.

[0390] After the completion of the reaction, the reaction solution was filtered through Celite, and washing with ethyl acetate was carried out. Water was then added to the filtrate, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0391] Methanol was added to the residue, followed by filtration to give the title compound as a crystal (27 mg, 29.7%).

MS m/z: 310

¹H-NMR δ: 4.19 (2H, d, J = 5.37 Hz), 5.09 (2H, s), 6.52 (1H, t, J = 7.32 Hz), 6.63 (1H, d, J = 7.32 Hz), 6.72 (1H,

t, J = 5.73 Hz), 6.97 (1H, dt, J = 1.46, 7.56 Hz), 7.04 (1H, d, J = 7.56 Hz), 7.59 (1H, dd, J = 1.95, 8.29 Hz), 7.67 (1H, d, J = 8.29 Hz), 8.01 (1H, d, J = 1.95 Hz), 9.28 (1H, s), 11.08 (1H, s)

Example 88: N-(2,4-Dichlorobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0392] Diphenylphosphoryl azide (162 mg, 0.59 mmol, 1.2 eq) and triethylamine (60 mg, 0.59 mmol, 1.2 eq) were added to a solution of 2,4-dichlorophenylacetic acid (101 mg, 0.49 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0393] Thereafter, 4-aminophthalimide (80 mg, 0.49 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0394] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate. The resultant crystal was washed with a chloroform/methanol solution to give the title compound as a crystal (9 mg, 5.0%).

MS m/z: 363, 365

¹H-NMR δ: 4.37 (2H, d, J = 4.88 Hz), 6.99 (1H, t, J = 5.22 Hz), 7.38 - 7.44 (2H, m), 7.57 - 7.63 (2H, m), 7.68 (1H, d, J = 8.29 Hz), 8.01 (1H, s), 9.46 (1H, s), 11.08 (1H, s)

Example 89: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(2,3,6-trichlorobenzyl)urea

[0395] Diphenylphosphoryl azide (162 mg, 0.59 mmol, 1.2 eq) and triethylamine (60 mg, 0.59 mmol, 1.2 eq) were added to a solution of 2,3,6-trichlorophenylacetic acid (118 mg, 0.49 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0396] Thereafter, 4-aminophthalimide (80 mg, 0.49 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0397] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (57 mg, 29.1%).

MS m/z: 397, 399

¹H-NMR δ: 4.63 - 4.66 (2H, m), 6.87 (1H, t, J = 5.24 Hz), 7.55 (1H, d, J = 8.54 Hz), 7.57 (1H, dd, J = 1.95, 8.05 Hz), 7.67 (2H, d, J = 8.54 Hz), 8.00 (1H, d, J = 1.71 Hz), 9.14 (1H, s), 11.09 (1H, s)

Example 90: N-(2,6-Difluorobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0398] Diphenylphosphoryl azide (162 mg, 0.59 mmol, 1.2 eq) and triethylamine (60 mg, 0.59 mmol, 1.2 eq) were added to a solution of 2,6-difluorophenylacetic acid (101 mg, 0.49 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0399] Thereafter, 4-aminophthalimide (80 mg, 0.49 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0400] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate. The resultant crystal was washed with a chloroform/methanol solution to give the title compound as a crystal (10 mg, 6.1%).

MS m/z: 331

¹H-NMR δ: 4.64 (2H, d, J = 4.64 Hz), 6.88 (1H, t, J = 5.73 Hz), 7.11 (2H, t, J = 8.05 Hz), 7.56 (1H, dd, J = 1.83, 8.29 Hz), 7.66 (1H, d, J = 8.29 Hz), 7.98 (1H, d, J = 1.71 Hz), 9.15 (1H, s), 11.08 (1H, s)

Example 91: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(2-fluoro-6-(trifluoromethyl)benzyl)urea

[0401] Diphenylphosphoryl azide (163 mg, 0.59 mmol, 1.2 eq) and triethylamine (60 mg, 0.59 mmol, 1.2 eq) were added to a solution of 2-fluoro-6-trifluoromethylphenylacetic acid (104 mg, 0.49 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0402] Thereafter, 4-aminophthalimide (80 mg, 0.49 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0403] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate. The resultant crystal was washed with a chloroform/methanol solution to give the title compound as a crystal (18 mg, 9.6%).

MS m/z: 381

¹H-NMR δ: 4.53 (2H, s), 6.74 (1H, t, J = 5.49 Hz), 7.55 (1H, dd, J = 1.71, 8.29 Hz), 7.60 - 7.64 (3H, m), 7.67 (1H, d, J = 8.29 Hz), 8.00 (1H, d, J = 1.71 Hz), 9.11 (1H, s), 11.09 (1H, s)

Example 92: N-Benzyl-N'-(4-pyridyl)urea

[0404] Toluene (1 ml) and a minor amount of DMF were added to 4-aminopyridine (50 mg, 0.53 mmol), and the mixture was heated. Thereafter, benzyl isocyanate (71 mg, 0.53 mmol, 1.0 eq) was added to the solution, and the mixture was stirred at 110°C for 120 min.

[0405] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (18 mg, 15.0%).

MS m/z: 227

¹H-NMR δ: 4.31 (2H, d, J = 5.85 Hz), 6.85 (1H, t, J = 5.85 Hz), 7.24 (1H, tt, J = 1.71, 6.83 Hz), 7.28 - 7.36 (4H, m), 7.37 (2H, dd, J = 1.56, 4.76 Hz), 8.28 (2H, d, J = 6.10 Hz), 9.01 (1H, s)

Example 93: N-(2-Nitrobenzyl)-N'-(4-pyridyl)urea

[0406] Diphenylphosphoryl azide (175 mg, 0.64 mmol, 1.2 eq) and triethylamine (65 mg, 0.64 mmol, 1.2 eq) were added to a solution of 2-nitrophenylacetic acid (96 mg, 0.53 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0407] Thereafter, 4-aminopyridine (50 mg, 0.53 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0408] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (25 mg, 17.4%).

MS m/z: 272, 273

¹H-NMR δ: 4.58 (2H, d, J = 6.10 Hz), 6.96 (1H, t, J = 6.10 Hz), 7.35 (2H, dd, J = 1.59, 4.76 Hz), 7.55 (1H, dt, J = 1.46, 7.80 Hz), 7.61 (1H, dd, J = 1.10, 7.68 Hz), 7.75 (1H, dt, J = 1.46, 7.56 Hz), 8.05 (1H, dd, J = 1.46, 8.17 Hz), 8.29 (2H, d, J = 6.34 Hz), 9.20 (1H, s)

Example 94: N-(2-Chlorobenzyl)-N'-(4-pyridyl)urea

[0409] Diphenylphosphoryl azide (175 mg, 0.64 mmol, 1.2 eq) and triethylamine (65 mg, 0.64 mmol, 1.2 eq) were added to a solution of 2-chlorophenylacetic acid (91 mg, 0.53 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0410] Thereafter, 4-aminopyridine (50 mg, 0.53 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0411] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (53 mg, 38.1%).

MS m/z: 262

¹H-NMR δ: 4.38 (2H, d, J = 6.10 Hz), 6.90 (1H, t, J = 5.85 Hz), 7.28 - 7.41 (4H, m), 7.37 (2H, dd, J = 1.46, 4.88 Hz), 7.45 (1H, dd, J = 1.46, 7.68 Hz), 8.29 (2H, dd, J = 1.46, 4.88 Hz), 9.13 (1H, s)

Example 95: N-(2,6-Difluorobenzyl)-N'-(1H-5-indazolyl)-urea

[0412] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 2,6-difluorophenylacetic acid (129 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0413] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0414] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (14 mg, 6.2%).

MS m/z: 302

¹H-NMR δ: 4.39 (2H, d, J = 5.85 Hz), 6.51 (1H, t, J = 5.73 Hz), 7.10 (2H, t, J = 8.17 Hz), 7.21 (1H, dd, J = 1.95, 8.78 Hz), 7.35 - 7.44 (2H, m), 7.83 (1H, d, J = 1.22 Hz), 7.92 (1H, d, J = 0.98 Hz), 8.36 (1H, s), 12.83 (1H, s)

Example 96: N-[2-fluoro-6-(trifluoromethyl)benzyl]-N'-(1H-5-indazolyl)urea

[0415] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 2-fluoro-6-trifluorophenylacetic acid (158 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0416] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0417] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (12 mg, 4.5%).

MS m/z: 352

¹H-NMR δ: 4.52 (2H, d, J = 5.12 Hz), 6.36 (1H, t, J = 5.37 Hz), 7.21 (1H, dd, J = 1.83, 8.78 Hz), 7.40 (1H, d, J = 8.78 Hz), 7.59 - 7.64 (3H, m), 7.84 (1H, d, J = 1.22 Hz), 8.35 (1H, s), 12.84 (1H, s)

Example 97: N-(2,3,4,5,6-Pentafluorobenzyl)-N'-(4-pyridyl)urea

[0418] Diphenylphosphoryl azide (146 mg, 0.53 mmol, 1.2 eq) and triethylamine (54 mg, 0.53 mmol, 1.2 eq) were added to a solutoin of 2,3,4,5,6-pentafluorophenylacetic acid (100 mg, 0.44 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0419] Thereafter, 4-aminopyridine (42 mg, 0.44 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0420] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (52 mg, 36.9%).

MS m/z: 317

¹H-NMR δ: 4.43 (2H, d, J = 4.88 Hz), 7.01 (1H, t, J = 5.73 Hz), 7.34 (2H, dd, J = 1.46, 4.88 Hz), 8.28 (2H, d, J = 6.34 Hz), 9.00 (1H, s)

Example 98: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(2,3,4,5,6-pentafluorobenzyl)urea

[0421] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 2,3,4,5,6-pentafluorophenylacetic acid (158 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0422] Thereafter, 4-aminophthalimide (59 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0423] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (12 mg, 7.0%).

MS m/z: 385

¹H-NMR δ: 4.45 (2H, d, J = 5.12 Hz), 7.07 (1H, t, J = 5.98 Hz), 7.58 (1H, dd, J = 1.71, 8.05 Hz), 7.66 (1H, d, J = 8.05 Hz), 7.97 (1H, d, J = 1.95 Hz), 9.30 (1H, s), 11.09 (1H, s)

Example 99: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(2,4,6-trifluorobenzyl)urea

[0424] Diphenylphosphoryl azide (198 mg, 0.72 mmol, 1.2 eq) and triethylamine (73 mg, 0.72 mmol, 1.2 eq) were added to a solution of 2,4,6-trifluorophenylacetic acid (114 mg, 0.60 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0425] Thereafter, 4-aminophthalimide (97 mg, 0.60 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0426] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (97 mg, 46.4%).

MS m/z: 349

¹H-NMR δ: 4.36 (2H, d, J = 4.64 Hz), 6.91 (1H, t, J = 5.73 Hz), 7.19 (2H, t, J = 8.66 Hz), 7.57 (1H, dd, J = 1.71, 8.05 Hz), 7.66 (1H, d, J = 8.29 Hz), 7.98 (1H, d, J = 1.71 Hz), 9.17 (1H, s), 11.08 (1H, s)

Example 100: N-(2,4-Dichlorobenzyl)-N'-(1H-5-indazolyl)-urea

[0427] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 2,4-dichlorophenylacetic acid (154 mg, 0.75 mmol) in toluene, and the mixture was stirred at

110°C for 60 min.

[0428] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0429] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (12 mg, 4.8%).

MS m/z: 334, 336

¹H-NMR δ: 4.35 (2H, d, J = 5.86 Hz), 6.64 (1H, t, J = 5.86 Hz), 7.26 (1H, dd, J = 1.71, 8.90 Hz), 7.39 - 7.47 (3H, m), 7.61 (1H, d, J = 1.71 Hz), 7.85 (1H, s), 7.93 (1H, s), 8.63 (1H, s), 12.85 (1H, s)

10 Example 101: N-(1H-5-Indazolyl)-N'-(2,3,6-trichlorobenzyl)urea

[0430] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 2,3,6-trichlorophenylacetic acid (180 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0431] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0432] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (10 mg, 3.6%).

MS m/z: 368, 370

¹H-NMR δ: 4.62 (2H, d, J = 5.37 Hz), 6.51 (1H, t, J = 5.49 Hz), 7.21 (1H, d, J = 8.78 Hz), 7.40 (1H, d, J = 9.03 Hz), 7.55 (1H, d, J = 8.78 Hz), 7.66 (1H, d, J = 8.78 Hz), 7.85 (1H, s), 7.93 (1H, s), 8.38 (1H, s), 12.84 (1H, s)

Example 102: N-(2-Chloro-6-fluorobenzyl)-N'-(1H-5-indazolyl)urea

[0433] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 2-chloro-6-fluorophenylacetic acid (142 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0434] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0435] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (12 mg, 5.0%).

MS m/z: 317, 319

¹H-NMR δ: 4.47 (2H, d, J = 5.61 Hz), 6.48 (1H, t, J = 5.61 Hz), 7.18 - 7.28 (2H, m), 7.34 - 7.43 (3H, m), 7.84 (1H, s), 7.92 (1H, s), 8.39 (1H, s), 12.84 (1H, s)

35 Example 103: N-(1H-5-Indazolyl)-N'-(2,4,6-trifluorobenzyl)urea

[0436] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 2,4,6-trifluorophenylacetic acid (143 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0437] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0438] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (23 mg, 9.6%).

MS m/z: 320

¹H-NMR δ: 4.34 (2H, d, J = 5.61 Hz), 6.53 (1H, t, J = 5.86 Hz), 7.18 (2H, t, J = 8.78 Hz), 7.21 (1H, dd, J = 1.95, 8.78 Hz), 7.39 (1H, d, J = 9.03 Hz), 7.82 (1H, d, J = 0.98 Hz), 7.92 (1H, s), 8.36 (1H, s), 8.36 (1H, s), 12.83 (1H, s)

50 Example 104: N-(2-Chlorobenzyl)-N'-(1H-5-indazolyl)urea

[0439] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 2-chlorophenylacetic acid (128 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0440] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0441] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (19 mg, 8.4%).

MS m/z: 300

¹H-NMR δ: 4.38 (2H, d, J = 5.61 Hz), 6.60 (1H, t, J = 5.98 Hz), 7.25 - 7.37 (3H, m), 7.39 - 7.44 (2H, m), 7.45 (1H, dd, J = 1.46, 7.81 Hz), 7.85 (1H, s), 7.93 (1H, s), 8.59 (1H, s), 12.84 (1H, s)

Example 105: N-Cyclohexylmethyl-N'-(1H-5-indazolyl)urea

[0442] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of cyclohexylacetic acid (107 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0443] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0444] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (15 mg, 7.4%).

MS m/z: 272

¹H-NMR δ: 0.91 (2H, q, J = 11.22 Hz), 1.10 - 1.26 (2H, m), 1.32 - 1.44 (1H, m), 1.59 - 1.74 (6H, m), 2.95 (2H, t,

J = 5.86 Hz), 6.07 (1H, t, J = 5.73 Hz), 7.23 (1H, d, J = 9.03 Hz), 7.39 (1H, d, J = 8.78 Hz), 7.83 (1H, s), 7.92 (1H, s), 8.28 (1H, s), 12.82 (1H, s)

Example 106: N-(2,6-Dichlorobenzyl)-N'-(1H-5-indazolyl)-urea

[0445] Diphenylphosphoryl azide (198 mg, 0.72 mmol, 1.2 eq) and triethylamine (73 mg, 0.72 mmol, 1.2 eq) were added to a solution of 2,6-dichlorophenylacetic acid (123 mg, 0.60 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0446] Thereafter, 5-aminoindazole (80 mg, 0.60 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 2.5 hr.

[0447] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (7 mg, 3.5%).

MS m/z: 334, 336

¹H-NMR δ: 4.58 (2H, d, J = 4.88 Hz), 6.40 (1H, t, J = 5.24 Hz), 7.21 (1H, dd, J = 1.83, 8.90 Hz), 7.34 - 7.42 (2H, m), 7.51 (2H, d, J = 8.05 Hz), 7.85 (1H, s), 7.93 (1H, s), 8.38 (1H, s), 12.84 (1H, s)

Example 107: N-(1H-5-Indazolyl)-N'-(1-naphthylmethyl)-urea

[0448] Diphenylphosphoryl azide (248 mg, 0.90 mmol, 1.2 eq) and triethylamine (91 mg, 0.90 mmol, 1.2 eq) were added to a solution of 1-naphthylacetic acid (140 mg, 0.75 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0449] Thereafter, 5-aminoindazole (100 mg, 0.75 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0450] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (20 mg, 8.4%).

MS m/z: 316

¹H-NMR δ: 4.78 (2H, d, J = 5.61 Hz), 5.78 (1H, t, J = 5.61 Hz), 7.26 (1H, dd, J = 1.95, 8.78 Hz), 7.41 (1H, d, J = 8.78 Hz), 7.47 - 7.62 (4H, m), 7.84 - 7.88 (2H, m), 7.93 - 7.98 (2H, m), 8.16 (1H, d, J = 8.29 Hz), 8.45 (1H, s), 12.85 (1H, s)

Example 108: N-(Pyridyl)-N'-(2,3,6-trifluorobenzyl)urea

[0451] Diphenylphosphoryl azide (173 mg, 0.63 mmol, 1.2 eq) and triethylamine (64 mg, 0.63 mmol, 1.2 eq) were added to a solution of 2,3,6-trifluorophenylacetic acid (100 mg, 0.53 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0452] Thereafter, 4-aminopyridine (50 mg, 0.53 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0453] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (62 mg, 42.2%).

MS m/z: 281

¹H-NMR δ: 4.41 (2H, d, J = 5.61 Hz), 6.94 (1H, t, J = 5.86 Hz), 7.10 - 7.17 (1H, m), 7.34 (2H, dd, J = 1.59, 4.76 Hz), 7.42 - 7.47 (1H, m), 8.28 (2H, dd, J = 1.46, 4.88 Hz), 8.94 (1H, s)

Example 109: N-(1,3-Dioxo-2,3-dihydro-1H-5-isoindolyl)-N'-(2,3,6-trifluorobenzyl)urea

[0454] Diphenylphosphoryl azide (173 mg, 0.63 mmol, 1.2 eq) and triethylamine (64 mg, 0.63 mmol, 1.2 eq) were added to a solution of 2,3,6-trifluorophenylacetic acid (100 mg, 0.53 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0455] Thereafter, 4-aminophthalimide (85 mg, 0.53 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0456] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give the title compound as a crystal (100 mg, 54.6%).

10 MS m/z: 349

¹H-NMR δ: 4.43 (2H, d, J = 5.37 Hz), 6.98 (1H, t, J = 5.86 Hz), 7.11 - 7.18 (1H, m), 7.40 - 7.50 (1H, m), 7.58 (1H, dd, J = 1.83, 8.05 Hz), 7.66 (1H, d, J = 8.05 Hz), 7.98 (1H, d, J = 1.46 Hz), 9.21 (1H, s), 11.08 (1H, s)

Example 110: N-(1H-5-Indazolyl)-N'-(2,3,6-trifluorobenzyl)urea

[0457] Diphenylphosphoryl azide (173 mg, 0.63 mmol, 1.2 eq) and triethylamine (64 mg, 0.63 mmol, 1.2 eq) were added to a solution of 2,3,6-trifluorophenylacetic acid (100 mg, 0.53 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0458] Thereafter, 5-aminoindazole (70 mg, 0.53 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0459] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate as a crystal (15 mg, 8.9%).

MS m/z: 320

¹H-NMR δ: 4.41 (2H, d, J = 5.61 Hz), 6.62 (1H, t, J = 5.86 Hz), 7.10 - 7.17 (1H, m), 7.21 (1H, dd, J = 1.83, 8.78

25 Hz), 7.40 (1H, d, J = 8.78 Hz), 7.40 - 7.48 (1H, m), 7.82 (1H, d, J = 1.71 Hz), 7.92 (1H, s), 8.41 (1H, s), 12.85 (1H, s)

Example 111: N-(3-Nitrobenzyl)-N'-(4-pyridyl)urea

[0460] Diphenylphosphoryl azide (182 mg, 0.66 mmol, 1.2 eq) and triethylamine (67 mg, 0.66 mmol, 1.2 eq) were added to a solution of 3-nitrophenylacetic acid (100 mg, 0.55 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0461] Thereafter, 4-aminopyridine (52 mg, 0.55 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0462] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound as a crystal (25 mg, 16.7%).

MS m/z: 273

¹H-NMR δ: 4.41 (2H, d, J = 6.10 Hz), 7.07 (1H, t, J = 5.98 Hz), 7.38 (2H, dd, J = 1.59, 4.76 Hz), 7.64 (1H, t, J =

40 7.81 Hz), 7.78 (1H, d, J = 7.81 Hz), 8.12 (1H, dd, J = 1.46, 8.05 Hz), 8.17 (1H, s), 8.29 (2H, dd, J = 1.46, 4.88 Hz), 9.19 (1H, s)

Example 112: N-(3-Aminobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea

[0463] Diphenylphosphoryl azide (182 mg, 0.66 mmol, 1.2 eq) and triethylamine (67 mg, 0.66 mmol, 1.2 eq) were added to a solution of 3-nitrophenylacetic acid (100 mg, 0.55 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

[0464] Thereafter, 4-aminophthalimide (89 mg, 0.55 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

[0465] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate. The resultant crystal was washed with chloroform/methanol to give a nitro compound (45 mg, 24.1%) containing a minor amount of 4-aminophthalimide as the starting compound.

[0466] DMF was added to the nitro compound (containing the starting compound, 40 mg, 0.12 mmol). Palladium hydroxide (one small spatula) was added thereto, and the mixture was stirred under a hydrogen atmosphere at room temperature for 60 min.

[0467] After the completion of the reaction, the reaction solution was filtered through Celite, and washing with ethyl acetate was carried out. Water was then added to the filtrate, and the mixture was extracted with ethyl acetate. The

ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give the title compound as a crystal (16 mg, 44.4%).

MS m/z: 310

- 5 $^1\text{H-NMR}$ δ : 4.17 (2H, d, J = 5.37 Hz), 5.03 (2H, s), 6.38 (1H, s), 6.44 (2H, d, J = 7.81 Hz), 6.51 (1H, s), 6.79 (1H, dd, J = 1.95, 8.05 Hz), 6.96 (1H, t, J = 7.68 Hz), 7.60 (1H, dd, J = 1.71, 8.29 Hz), 7.67 (1H, d, J = 8.29 Hz), 7.74 (1H, s), 8.03 (1H, d, J = 1.95 Hz), 11.08 (1H, s)

Example 113: N-(4-Hydroxy-3-methoxybenzyl)-N'-(1H-5-indazoly)urea

- 10 [0468] Diphenylphosphoryl azide (242 mg, 0.88 mmol, 1.2 eq) and triethylamine (89 mg, 0.88 mmol, 1.2 eq) were added to a solution of 4-benzyloxy-3-methoxyphenylacetic acid (200 mg, 0.73 mmol) in toluene, and the mixture was stirred at 110°C for 60 min.

- 15 [0469] Thereafter, 5-aminoindazole (98 mg, 0.73 mmol, 1.0 eq) and a minor amount of DMF were added thereto, and the mixture was stirred at 110°C for 3 hr.

- 20 [0470] After the completion of the reaction, water and ethyl acetate were added thereto, and the precipitated crystal was collected by filtration and was washed with ethyl acetate to give a crystal (26 mg, 8.8%).

- 25 [0471] Palladium hydroxide (one small spatula) was added to a solution of the resultant crystal (20 mg, 0.05 mmol) in DMF, and the mixture was stirred under a hydrogen atmosphere at room temperature for 60 min.

- 30 [0472] After the completion of the reaction, the reaction solution was filtered through Celite, and washing with ethyl acetate was carried out. Water was then added to the filtrate, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give the title compound as a crystal (8 mg, 53.3%).

MS m/z: 312

- 35 $^1\text{H-NMR}$ δ : 3.75 (3H, s), 5.69 (2H, d, J = 5.61 Hz), 6.39 (1H, t, J = 5.61 Hz), 6.72 (2H, s), 6.89 (1H, s), 7.25 (1H, dd, J = 1.83, 8.78 Hz), 7.40 (1H, d, J = 8.78 Hz), 7.85 (1H, s), 7.93 (1H, s), 8.40 (1H, s), 8.82 (1H, s), 12.84 (1H, s)

Example 114: N-[1-(3,4-Dichlorobenzyl)-4-piperidyl]-N-(1H-5-indazoly)amine

- 40 [0473] Potassium carbonate (138 mg, 1.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (77 mg, 0.50 mmol) and 3,4-dichlorobenzyl chloride (98 mg, 0.50 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 15 hr.

- 45 [0474] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

- 50 [0475] 5-Aminoindazole (53 mg, 0.40 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (56 mg, 0.60 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 18 hr.

- 55 [0476] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (100 mg, 53.2%).

MS m/z: 375

- 60 $^1\text{H-NMR}$ δ : 1.34 - 1.45 (2H, m), 1.94 (2H, d, J = 11.47 Hz), 2.12 (2H, t, J = 10.86 Hz), 2.77 (2H, d, J = 11.47 Hz), 3.12 - 3.30 (1H, m), 3.49 (2H, s), 5.10 (1H, d, J = 7.56 Hz), 6.67 (1H, s), 6.81 (1H, dd, J = 2.07, 8.90 Hz), 7.25 (1H, d, J = 8.78 Hz), 7.31 (1H, dd, J = 1.83, 8.17 Hz), 7.55 (1H, d, J = 1.95 Hz), 7.58 (1H, d, J = 8.05 Hz), 7.73 (1H, s), 12.55 (1H, s)

65 Example 115: N-[1-(3,4-Dimethylbenzyl)-4-piperidyl]-N-(1H-5-indazoly)amine

- 70 [0477] Potassium carbonate (138 mg, 1.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (77 mg, 0.50 mmol) and 3,4-dimethylbenzyl chloride (97 mg, 0.50 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

- 75 [0478] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

- 80 [0479] 5-Aminoindazole (53 mg, 0.40 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic

acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (56 mg, 0.60 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 4 hr.

[0480] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (45 mg, 26.9%).

MS m/z: 335

¹H-NMR δ: 1.32 - 1.45 (2H, m), 1.94 (2H, d, J = 11.71 Hz), 2.19 (3H, s), 2.13 - 2.18 (2H, m), 2.21 (3H, s), 2.76 - 2.87 (2H, m), 3.15 - 3.25 (1H, m), 3.43 (2H, s), 5.07 - 5.19 (1H, m), 6.66 (1H, s), 6.81 (1H, dd, J = 1.95, 8.78 Hz), 7.01 (1H, d, J = 7.07 Hz), 7.07 (1H, s), 7.08 (1H, d, J = 7.07), 7.25 (1H, d, J = 8.78 Hz), 7.73 (1H, s), 12.55 (1H, s)

Example 116: N-(1H-5-Indazolyl)-N-[1-(2-naphthylmethyl)-4-piperidyl]amine

[0481] Potassium carbonate (138 mg, 1.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (77 mg, 0.50 mmol) and 2-(bromomethyl)naphthalene (110 mg, 0.50 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

[0482] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0483] 5-Aminoindazole (53 mg, 0.40 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (56 mg, 0.60 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 15 hr.

[0484] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (98 mg, 54.9%).

MS m/z: 357

¹H-NMR δ: 1.37 - 1.50 (2H, m), 1.92 - 2.01 (2H, m), 2.13 - 2.22 (2H, m), 2.83 - 2.95 (2H, m), 3.18 - 3.29 (1H, m), 3.63 - 3.76 (2H, m), 5.10 - 5.15 (1H, m), 6.67 (1H, s), 6.82 (1H, dd, J = 1.95, 8.78 Hz), 7.25 (1H, d, J = 8.78 Hz), 7.46 - 7.54 (3H, m), 7.73 (1H, s), 7.81 (1H, s), 7.86 - 7.92 (3H, m), 12.55 (1H, s)

Example 117: N-[1-(3-Fluorobenzyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0485] Potassium carbonate (276 mg, 2.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (154 mg, 1.0 mmol) and 3-fluorobenzyl chloride (145 mg, 1.0 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

[0486] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0487] 5-Aminoindazole (106 mg, 0.80 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (112 mg, 1.20 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 15 hr.

[0488] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (195 mg, 60.0%).

MS m/z: 324

¹H-NMR δ: 1.34 - 1.45 (2H, m), 1.94 (2H, d, J = 11.22 Hz), 2.11 (2H, t, J = 10.73 Hz), 2.79 (2H, d, J = 11.71 Hz), 3.15 - 3.27 (1H, m), 3.50 (2H, s), 5.10 (1H, d, J = 8.05 Hz), 6.66 (1H, s), 6.81 (1H, dd, J = 1.95, 9.03 Hz), 7.63 (1H, dt, J = 2.68, 8.78 Hz), 7.12 (1H, d, J = 8.78 Hz), 7.15 (1H, d, J = 7.56 Hz), 7.25 (1H, d, J = 8.78 Hz), 7.36 (1H, q, J = 7.34 Hz), 7.72 (1H, s), 12.55 (1H, s)

Example 118: N-(1H-5-Indazolyl)-N-[1-[4-(trifluoromethyl)benzyl]-4-piperidyl]amine

[0489] Potassium carbonate (276 mg, 2.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (154 mg, 1.0 mmol) and 4-trifluoromethylbenzyl chloride (239 mg, 1.0 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

[0490] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0491] 5-Aminoindazole (106 mg, 0.80 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (112 mg, 1.20 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 15 hr.

[0492] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (210 mg, 62.4%).

MS m/z: 374

¹H-NMR δ: 1.35 - 1.46 (2H, m), 1.95 (2H, d, J = 10.98 Hz), 2.14 (2H, t, J = 11.22 Hz), 2.79 (2H, d, J = 11.22 Hz), 3.12 - 3.24 (1H, m), 3.58 (2H, s), 5.11 (1H, d, J = 8.05 Hz), 6.67 (1H, s), 6.82 (1H, dd, J = 2.07, 8.78 Hz), 7.25 (1H, d, J = 8.78 Hz), 7.54 (2H, d, J = 8.05 Hz), 7.69 (2H, d, J = 8.05 Hz), 7.73 (1H, s), 12.55 (1H, s)

Example 119: N-(1H-5-Indazolyl)-N-[1-(3-methoxybenzyl)-4-piperidyl]amine

[0493] Potassium carbonate (276 mg, 2.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (154 mg, 1.0 mmol) and 3-methoxybenzyl chloride (157 mg, 1.0 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

[0494] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0495] 5-Aminoindazole (106 mg, 0.80 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (112 mg, 1.20 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 15 hr.

[0496] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (167 mg, 49.6%).

MS m/z: 336

¹H-NMR δ: 1.38 - 1.48 (2H, m), 1.92 - 2.00 (2H, m), 2.20 - 2.31 (2H, m), 2.68 - 2.90 (2H, m), 3.20 - 3.28 (1H, m), 3.48 - 3.70 (2H, m), 3.75 (3H, s), 5.10 - 5.17 (1H, m), 6.67 (1H, s), 6.81 (1H, dd, J = 1.95, 9.03 Hz), 6.83 - 6.93 (3H, m), 7.22 - 7.28 (2H, m), 7.73 (1H, s), 12.56 (1H, s)

Example 120: N-[1-(4-Ethylbenzyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0497] Potassium carbonate (276 mg, 2.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (154 mg, 1.0 mmol) and 4-ethylbenzyl chloride [containing 30% of 2-position isomer] (155 mg, 1.0 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

[0498] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

[0499] 5-Aminoindazole (106 mg, 0.80 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (112 mg, 1.20 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 15 hr.

[0500] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and

saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (105 mg, 31.4%).

MS m/z: 334

⁵ ¹H-NMR δ: 1.34 (3H, t, J = 7.56 Hz), 1.47 - 1.59 (2H, m), 2.09 (2H, d, J = 11.71 Hz), 2.19 (2H, t, J = 10.49 Hz), 2.90 (2H, d, J = 11.95 Hz), 3.28 - 3.37 (1H, m), 3.54 (2H, s), 6.79 (1H, dd, J = 2.20, 8.29 Hz), 6.81 (1H, s), 7.16 (2H, d, J = 8.05 Hz), 7.25 (2H, d, J = 8.05 Hz), 7.29 (1H, d, J = 8.78 Hz), 7.87 (1H, d, J = 0.98 Hz)

Example 121: N-[1-(2-Ethylbenzyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

¹⁰ [0501] In the purification of the compound of Example 120 by column chromatography [silica gel, chloroform/methanol], the 2-position isomer stemmed from the starting compound was obtained (52 mg, 15.5%).

MS m/z: 334

¹⁵ ¹H-NMR δ: 1.23 (3H, t, J = 7.44 Hz), 1.43 - 1.55 (2H, m), 2.07 (2H, d, J = 11.95 Hz), 2.21 (2H, t, J = 10.86 Hz), 2.74 (2H, q, J = 7.48 Hz), 2.89 (2H, d, J = 11.71 Hz), 3.29 - 3.39 (1H, m), 3.54 (2H, s), 6.78 (1H, dd, J = 2.07, 8.66 Hz), 6.81 (1H, d, J = 1.71 Hz), 7.11 - 7.25 (3H, m), 7.26 (1H, d, J = 7.81 Hz), 7.32 (1H, d, J = 7.32 Hz), 7.88 (1H, d, J = 0.98 Hz)

Example 122: N-(1H-5-Indazolyl)-N-[1-(4-isopropylbenzyl)-4-piperidyl]amine

²⁰ [0502] Potassium carbonate (276 mg, 2.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (154 mg, 1.0 mmol) and 4-isopropylbenzyl chloride [containing 10% of 2-position isomer] (169 mg, 1.0 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

²⁵ [0503] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

³⁰ [0504] 5-Aminoindazole (106 mg, 0.80 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (112 mg, 1.20 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 15 hr.

³⁵ [0505] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (88 mg, 25.2%).

MS m/z: 348

⁴⁰ ¹H-NMR δ: 1.24 (3H, s), 1.26 (3H, s), 1.45 - 1.56 (2H, m), 2.08 (2H, d, J = 12.20 Hz), 2.18 (2H, t, J = 11.34 Hz), 2.86 - 2.29 (3H, m), 3.27 - 3.36 (1H, m), 3.52 (2H, s), 6.80 (1H, dd, J = 2.20, 9.03 Hz), 6.81 (1H, s), 7.18 (2H, d, J = 8.05 Hz), 7.25 (2H, d, J = 8.78 Hz), 7.28 (1H, d, J = 8.54 Hz), 7.87 (1H, d, J = 0.98 Hz)

Example 123: N-(1H-5-Indazolyl)-N-[1-(3-phenoxybenzyl)-4-piperidyl]amine

⁴⁵ [0506] Potassium carbonate (276 mg, 2.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (154 mg, 1.0 mmol) and 3-phenoxybenzyl chloride (219 mg, 1.0 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

⁵⁰ [0507] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

⁵⁵ [0508] 5-Aminoindazole (106 mg, 0.80 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (112 mg, 1.20 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 15 hr.

⁶⁰ [0509] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (164 mg, 41.1%).

MS m/z: 398

¹H-NMR δ: 1.44 - 1.56 (2H, m), 2.08 (2H, d, J = 12.20 Hz), 2.13 - 2.23 (2H, m), 2.87 (2H, d, J = 11.47 Hz), 3.27 - 3.35 (1H, m), 3.53 (2H, s), 6.80 (1H, dd, J = 2.20, 8.05 Hz), 6.81 (1H, s), 6.89 (1H, dd, J = 1.71, 8.05 Hz), 6.99 - 7.12 (5H, m), 7.27 - 7.36 (4H, m), 7.87 (1H, d, J = 0.98 Hz)

5 Example 124: N-(1H-5-Indazolyl)-N-[1-(4-methyl-3-nitrobenzyl)-5-piperidyl]amine

[0510] Potassium carbonate (276 mg, 2.0 mmol, 2.0 eq) was added to a solution of 4-piperidone monohydrate hydrochloride (154 mg, 1.0 mmol) and 4-methyl-3-nitrobenzyl chloride (186 mg, 1.0 mmol, 1.0 eq) in acetonitrile, and the mixture was stirred at room temperature for 17 hr.

10 [0511] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure.

15 [0512] 5-Aminoindazole (106 mg, 0.80 mmol, 0.8 eq) was added to a solution of the resultant oil in methanol. Acetic acid (one drop) was added thereto, and the mixture was stirred at room temperature for 5 min. A borane-pyridine complex (112 mg, 1.20 mmol, 1.2 eq) was added thereto under ice cooling, and the mixture was stirred at room temperature for 15 hr.

20 [0513] After the completion of the reaction, the reaction solution was poured into an aqueous sodium hydrogencarbonate solution, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over sodium sulfate, and the solvent was then removed by distillation under the reduced pressure. The residue was washed with chloroform to give the title compound as a crystal (103 mg, 35.5%).

MS m/z: 366

25 ¹H-NMR δ: 1.34 - 1.46 (2H, m), 1.94 (2H, d, J = 10.98 Hz), 2.13 (2H, t, J = 10.37 Hz), 2.50 (3H, s), 2.79 (2H, d, J = 11.71 Hz), 3.14 - 3.26 (1H, m), 3.56 (2H, s), 5.11 (1H, d, J = 7.81 Hz), 6.67 (1H, s), 6.52 (1H, dd, J = 2.07, 8.78 Hz), 7.25 (1H, d, J = 8.78 Hz), 7.46 (1H, d, J = 7.81 Hz), 7.56 (1H, dd, J = 1.59, 7.81 Hz), 7.73 (1H, s), 7.91 (1H, d, J = 1.46 Hz), 12.55 (1H, s)

Example 125: N-(1-Ethyl-4-piperidyl)-N-(1H-5-indazolyl)-amine

30 [0514] 1-Ethyl-4-piperidone (76 mg), 5-aminoindazole (67 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (50 mg, yield 41%).

35 ¹H-NMR (CDCl₃, 400 MHz): 1.06 (t, J = 7.3 Hz, 3H), 1.42 - 1.53 (m, 2H), 2.02 - 2.17 (m, 4H), 2.42 (q, J = 7.1 Hz, 2H), 2.86 - 2.95 (m, 2H), 3.21 - 3.33 (m, 1H), 6.70 - 6.76 (m, 2H), 7.23 (d, J = 8.5 Hz, 1H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 245 (M⁺+1)

40 Example 126: N-(1-Benzyl-4-piperidyl)-N-(1H-5-indazolyl)amine

[0515] 1-Benzyl-4-piperidone (635 mg), 5-aminoindazole (532 mg), and acetic acid (0.20 ml) were dissolved in methanol (10 ml), and a borane-pyridine complex (0.51 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (1.00 g, yield 82%).

45 ¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.59 (m, 2H), 2.05 - 2.13 (m, 4H), 2.15 - 2.25 (m, 2H), 2.85 - 2.93 (m, 2H), 3.27 - 3.37 (m, 1H), 3.56 (s, 2H), 6.77 - 6.82 (m, 2H), 7.24 - 7.35 (m, 6H), 7.88 (s, 1H)

50 Mass spectrum (ESI-MS, m/z): 307 (M⁺+1)

Formation of salt of compound prepared in Example 126

55 [0516] The compound prepared in Example 126 was dissolved in hydrochloric acid-methanol, and the mixture was then allowed to stand at room temperature for 18 hr. The resultant white precipitate was then collected by filtration, was washed with methanol which had been cooled in an ice bath, and was dried under the reduced pressure to give the title compound.

Example 127: N-(1-Benzyl-4-piperidyl)-N-(1H-5-indazoly)amine hydrochloride

[0517] 1-Benzyl-4-piperidone (11.44 ml), 5-aminoindazole (10.42 g), and acetic acid (1 ml) were dissolved in methanol (100 ml), and a borane-pyridine complex (10.10 ml) was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (100 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. Hydrochloric acid-methanol (100 ml) was added to the residue. The mixture was allowed to stand at room temperature for 18 hr, and the resultant white precipitate was then collected by filtration, was washed with methanol which had been cooled in an ice bath, and was dried under the reduced pressure to give 18.86 g of the title compound.

¹H-NMR (DMSO-d₆, 400 MHz): 2.14 - 2.30 (m, 4H), 2.88 - 3.10 (m, 2H), 3.40 - 3.50 (m, 2H), 3.70 - 3.80 (m, 1H), 4.25 (s, 2H), 7.26 - 7.76 (m, 6H), 7.99 (s, 1H), 8.23 (s, 1H), 10.96 (s, 1H), 11.45 (s, 1H)

Mass spectrum (ESI-MS, m/z): 307 (M⁺⁺¹)

Example 128: N-(1H-5-Indazolyl)-N-(4-piperidyl)amine

[0518] tert-Butyl-4-oxo-1-piperidine carboxylate (796 mg), 5-aminoindazole (532 mg), and acetic acid (0.2 ml) were dissolved in methanol (10 ml), and a borane-pyridine complex (0.51 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give an intermediate (750 mg, yield 60%).

[0519] This intermediate (107 mg) was dissolved in chloroform (3 ml), and trifluoroacetic acid (2 ml) was added to the solution. The reaction mixture was stirred at room temperature for 3 hr and was then concentrated, and trifluoroacetic acid was removed. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to the residue, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give the title compound (24 mg, yield 56%).

¹H-NMR (CDCl₃, 400 MHz): 1.28 - 1.42 (m, 2H), 2.08 - 2.17 (m, 2H), 2.70 - 2.80 (m, 2H), 3.12 - 3.20 (m, 2H), 3.34 - 3.45 (m, 1H), 6.79 - 6.86 (m, 2H), 7.30 (d, J = 8.8 Hz, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 217 (M⁺⁺¹)

Example 129: N-Cyclohexyl-N-(1H-5-indazoly)amine

[0520] Cyclohexanone (59 mg), 5-aminoindazole (67 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (94 mg, yield 87%).

¹H-NMR (CDCl₃, 400 MHz): 1.12 - 1.30 (m, 3H), 1.33 - 1.46 (m, 2H), 1.62 - 1.72 (m, 1H), 1.72 - 1.83 (m, 2H), 3.22 - 3.31 (m, 1H), 6.78 - 6.84 (m, 2H), 7.29 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H)

Mass spectrum (FD, m/z): 215 (M⁺)

Example 130: N-(1H-5-Indazolyl)-N-(1-phenethyl-4-piperidyl)amine

[0521] 1-(2-Phenethyl)-4-piperidone (142 mg), 5-aminoindazole (67 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (104 mg, yield 65%).

¹H-NMR (CDCl₃, 400 MHz): 1.49 - 1.61 (m, 2H), 2.10 - 2.20 (m, 2H), 2.20 - 2.30 (m, 2H), 2.60 - 2.68 (m, 2H), 2.80 - 2.87 (m, 2H), 2.97 - 3.05 (m, 2H), 3.30 - 3.40 (m, 1H), 6.79 - 6.84 (m, 2H), 7.18 - 7.23 (m, 3H), 7.26 - 7.33 (m, 3H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 321 (M⁺⁺¹)

Example 131: N-(1H-5-Indazolyl)-N-[1-(2-pyridylmethyl)-4-piperidyl]amine

[0522] 2-(Chloromethyl)pyridine hydrochloride (82 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the solution was stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0523] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (85 mg, yield 55%)

¹H-NMR (CDCl₃, 400 MHz): 1.50 - 1.65 (m, 2H), 2.06 - 2.17 (m, 2H), 2.25 - 2.40 (m, 2H), 2.90 - 2.99 (m, 2H), 3.30 - 3.40 (m, 1H), 3.73 (s, 2H), 6.79 - 6.84 (m, 2H), 7.15 - 7.21 (m, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.88 (s, 1H), 8.58 (d, J = 4.2 Hz, 1H)

Mass spectrum (ESI-MS, m/z): 308 (M⁺+1)

Example 132: N-(1H-5-Indazolyl)-N-[1-(3-pyridylmethyl)-4-piperidyl]amine

[0524] 3-(Chloromethyl)pyridine hydrochloride (82 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the solution was stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0525] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (57 mg, yield 47%).

¹H-NMR (CDCl₃, 400 MHz): 1.43 - 1.52 (m, 2H), 2.05 - 2.14 (m, 2H), 2.16 - 2.26 (m, 2H), 2.82 - 2.91 (m, 2H), 3.28 - 3.38 (m, 1H), 3.55 (s, 2H), 6.78 - 6.84 (m, 2H), 7.24 - 7.27 (m, 1H), 7.29 (d, J = 9.5 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.88 (s, 1H), 8.52 (d, J = 4.6 Hz, 1H), 8.56 (s, 1H)

Mass spectrum (ESI-MS, m/z): 308 (M⁺+1)

Example 133: N-(1H-5-Indazolyl)-M-[1-(4-pyridylmethyl)-4-piperidyl]amine

[0526] 4-(Chloromethyl)pyridine hydrochloride (82 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the solution was stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0527] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (49 mg, yield 40%).

¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.59 (m, 2H), 2.06 - 2.15 (m, 2H), 2.17 - 2.29 (m, 2H), 2.80 - 2.90 (m, 2H), 3.29 - 3.39 (m, 1H), 3.54 (s, 2H), 6.79 - 6.84 (m, 2H), 7.26 - 7.32 (m, 3H), 7.88 (s, 1H), 8.55 (d, J = 6.1 Hz, 2H)

Mass spectrum (ESI-MS, m/z): 308 (M⁺+1)

Example 134: N-[1-(2-Chlorobenzyl)-4-piperidyl]-N-(1H-5 indazolyl)amine

[0528] 2-Chlorobenzyl chloride (81 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0529] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (109 mg, yield 80%).

¹H-NMR (CDCl₃, 400 MHz): 1.47 - 1.60 (m, 2H), 2.06 - 2.16 (m, 2H), 2.25 - 2.36 (m, 2H), 2.87 - 2.97 (m, 2H), 3.30 - 3.40 (m, 1H), 3.67 (s, 2H), 6.78 - 6.84 (m, 2H), 7.16 - 7.34 (m, 4H), 7.35 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 6.8 Hz, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 341 (M⁺+1)

5

Example 135: N-[1-(3-Chlorobenzyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0530] 3-Chlorobenzyl chloride (81 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0531] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (104 mg, yield 79%).

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.58 (m, 2H), 2.05 - 2.14 (m, 2H), 2.15 - 2.25 (m, 2H), 2.82 - 2.90 (m, 2H), 3.28 - 3.37 (m, 1H), 3.52 (s, 2H), 6.78 - 6.83 (m, 2H), 7.18 - 7.26 (m, 3H), 7.29 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 341 (M⁺+1)

20

Example 136: N-[1-(4-Chlorobenzyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0532] 4-Chlorobenzyl chloride (81 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0533] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (106 mg, yield 79%).

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.59 (m, 2H), 2.05 - 2.13 (m, 2H), 2.13 - 2.25 (m, 2H), 2.81 - 2.91 (m, 2H), 3.25 - 3.37 (m, 1H), 3.51 (s, 2H), 6.78 - 6.82 (m, 2H), 7.27 - 7.32 (m, 6H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 341 (M⁺+1)

35

Example 137: N-[1-(4-Fluorobenzyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0534] 4-Fluorobenzyl chloride (72 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0535] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (102 mg, yield 79%).

¹H-NMR (CDCl₃, 400 MHz): 1.44 - 1.58 (m, 2H), 2.05 - 2.13 (m, 2H), 2.12 - 2.23 (m, 2H), 2.82 - 2.92 (m, 2H), 3.27 - 3.37 (m, 1H), 3.51 (s, 2H), 6.78 - 6.82 (m, 2H), 6.97 - 7.05 (m, 2H), 7.26 - 7.32 (m, 4H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 325 (M⁺+1)

50

Example 138: N-(1H-5-Indazolyl)-N-[1-(4-methoxybenzyl)-4-piperidyl]amine

[0536] 4-Methoxybenzyl chloride (79 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0537] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then

added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (100 mg, yield 74%).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.43 - 1.56 (m, 2H), 2.03 - 2.13 (m, 2H), 2.12 - 2.22 (m, 2H), 2.83 - 2.92 (m, 2H),

3.26 - 3.36 (m, 1H), 3.50 (s, 2H), 3.81 (s, 3H), 6.77 - 6.82 (m, 2H), 6.86 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 9.0 Hz, 1H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 337 (M⁺⁺1)

Example 139: N-(1H-5-Indazolyl)-N-[1-(4-methylbenzyl)-4-piperidyl]amine

¹⁰ [0538] 4-Methylbenzyl chloride (71 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0539] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (100 mg, yield 76%).

²⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.44 - 1.57 (m, 2H), 2.03 - 2.13 (m, 2H), 2.12 - 2.23 (m, 2H), 2.34 (s, 3H), 2.84 - 2.92 (m, 2H), 3.25 - 3.36 (m, 1H), 3.52 (s, 2H), 6.77 - 6.82 (m, 2H), 7.13 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 321 (M⁺⁺1)

Example 140: N-(1H-5-Indazolyl)-N-[1-(3-nitrobenzyl)-4-piperidyl]amine

[0540] 3-Nitrobenzyl chloride (86 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0541] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (91 mg, yield 65%).

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.60 (m, 2H), 2.07 - 2.15 (m, 2H), 2.18 - 2.32 (m, 2H), 2.82 - 2.92 (m, 2H), 3.30 - 3.40 (m, 1H), 3.63 (s, 2H), 6.79 - 6.84 (m, 2H), 7.31 (d, J = 9.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.1 Hz, 1H), 7.88 (s, 1H), 8.12 (d, J = 6.9 Hz, 1H), 8.23 (s, 1H)

Example 141: N-(1H-5-Indazolyl)-N-[1-(4-nitrobenzyl)-4-piperidyl]amine

[0542] 4-Nitrobenzyl chloride (86 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0543] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (92 mg, yield 65%).

¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.58 (m, 2H), 2.06 - 2.15 (m, 2H), 2.15 - 2.30 (m, 2H), 2.80 - 2.90 (m, 2H), 3.29 - 3.40 (m, 1H), 3.63 (s, 2H), 6.79 - 6.83 (m, 2H), 7.31 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.88 (s, 1H), 8.19 (d, J = 8.8 Hz, 2H)

Example 142: N-[1-[4-(Benzylxyloxy)benzyl]-4-piperidyl]-N-(1H-5-indazolyl)amine

[0544] 4-Benzylxyloxybenzyl chloride (116 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr.

The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0545] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (124 mg, yield 75%).

¹H-NMR (CDCl₃, 400 MHz): 1.44 - 1.57 (m, 2H), 2.04 - 2.12 (m, 2H), 2.12 - 2.22 (m, 2H), 2.83 - 2.92 (m, 2H), 3.26 - 3.36 (m, 1H), 3.49 (s, 2H), 5.06 (s, 2H), 6.77 - 6.82 (m, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 7.25 - 7.46 (m, 6H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 413 (M⁺+1)

Example 143: N-[1-(3,5-Dimethoxybenzyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0546] 3,5-Dimethoxybenzyl chloride (94 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0547] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (102 mg, yield 69%).

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.59 (m, 2H), 2.04 - 2.13 (m, 2H), 2.14 - 2.25 (m, 2H), 2.84 - 2.94 (m, 2H), 3.27 - 3.37 (m, 1H), 3.49 (s, 2H), 3.79 (s, 6H), 6.35 - 6.39 (m, 1H), 6.50 - 6.54 (m, 2H), 6.78 - 6.83 (m, 2H), 7.26 - 7.31 (m, 1H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 367 (M⁺+1)

Example 144: N-{1-[(6-Chloro-1,3-benzodioxol-5-yl)methyl]-4-piperidyl}-N-(1H-5-indazolyl)amine

[0548] 6-Chloropiperonyl chloride (103 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0549] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (120 mg, yield 78%).

¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.58 (m, 2H), 2.05 - 2.14 (m, 2H), 2.22 - 2.33 (m, 2H), 2.85 - 2.93 (m, 2H), 3.29 - 3.39 (m, 1H), 3.56 (s, 2H), 5.96 (s, 2H), 6.79 - 6.84 (m, 3H), 7.00 (s, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 385 (M⁺+1)

Example 145: 4-[(4-(1H-5-Indazolylamino)piperidino)-methyl]phenol

[0550] N-{1-[4-(Benzylxy)benzyl]-4-piperidyl}-N-(1H-5-indazolyl)amine (Example 142, 33 mg) and palladium-charcoal (10 mg) were suspended in ethanol (3 ml), and the suspension was stirred under a hydrogen atmosphere of 1 atm at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give the title compound (21 mg, yield 82%).

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.55 (m, 2H), 2.04 - 2.20 (m, 4H), 2.83 - 2.91 (m, 2H), 3.25 - 3.35 (m, 1H), 3.47 (s, 2H), 6.70 - 6.83 (m, 3H), 6.76 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.8 Hz, 1H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 323 (M⁺+1)

Example 146: N-(1-Benzyltetrahydro-1H-pyrrolyl)-N-(1H-5-indazolyl)amine

[0551] 1-Benzyl-3-pyrrolidinone (105 mg), 5-aminoindazole (67 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate so-

lution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (49 mg, yield 34%).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.66 - 1.78 (m, 1H), 2.30 - 2.41 (m, 1H), 2.44 - 2.53 (m, 1H), 2.61 - 2.68 (m, 1H), 2.77 - 2.87 (m, 2H), 3.66 (s, 2H), 4.00 - 4.08 (m, 1H), 6.73 - 6.76 (m, 1H), 6.77 - 6.83 (m, 1H), 7.24 - 7.36 (m, 6H), 7.88 (s, 1H)

¹⁰ Mass spectrum (ESI-MS, m/z): 293 (M⁺+1)

Formation of salt of compound prepared in Example 146

¹⁵ [0552] The compound prepared in Example 146 was dissolved in hydrochloric acid-methanol, and the mixture was then allowed to stand at room temperature for 18 hr. The resultant white precipitate was then collected by filtration, was washed with methanol which had been cooled in an ice bath, and was dried under the reduced pressure to give the title compound.

Example 147: Methyl 3-[(4-(1H-5-indazolylamino)-piperidino)methyl]benzoate

²⁰ [0553] Methyl 3-(chloromethyl)benzoate (92 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

²⁵ [0554] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (62 mg, yield 44%).

³⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.58 (m, 2H), 2.05 - 2.14 (m, 2H), 2.16 - 2.28 (m, 2H), 2.83 - 2.91 (m, 2H), 3.26 - 3.37 (m, 1H), 3.60 (s, 2H), 3.92 (s, 3H), 6.78 - 6.83 (m, 2H), 7.29 (d, J = 9.0 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.99 (s, 1H)

³⁵ Mass spectrum (ESI-MS, m/z): 365 (M⁺+1)

Example 148: Methyl 4-[(4-(1H-5-indazolylamino)-piperidino)methyl]benzoate

⁴⁰ [0555] Methyl 4-(chloromethyl)benzoate (92 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

⁴⁵ [0556] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (51 mg, yield 35%).

⁵⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.58 (m, 2H), 2.05 - 2.14 (m, 2H), 2.16 - 2.27 (m, 2H), 2.82 - 2.92 (m, 2H), 3.29 - 3.38 (m, 1H), 3.60 (s, 2H), 3.91 (s, 3H), 6.78 - 6.83 (m, 2H), 7.30 (d, J = 9.8 Hz, 1H), 7.42 (t, J = 8.1 Hz, 2H), 7.87 (s, 1H), 7.99 (d, J = 8.3 Hz, 2H)

⁵⁵ Mass spectrum (ESI-MS, m/z): 365 (M⁺+1)

Example 149: 4-[(4-(1H-5-Indazolylamino)piperidino)-methyl]phenyl acetate

⁶⁰ [0557] 4-(Chloromethyl)phenyl acetate (92 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

⁶⁵ [0558] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (33 mg, yield 23%).

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.70 (m, 2H), 2.01 - 2.20 (m, 2H), 2.20 - 2.28 (m, 2H), 2.30 (s, 3H), 2.85 - 2.94 (m, 2H), 3.28 - 3.38 (m, 1H), 3.55 (s, 2H), 6.78 - 6.83 (m, 2H), 7.04 (d, J = 8.5, 2H), 7.29 (d, J = 9.8 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 365 (M⁺+1)

5

Example 150: N-[1-(2-Chloro-6-fluorobenzyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0559] 2-Chloro-6-fluorobenzyl chloride (89 mg), 4-piperidone monohydrate hydrochloride (77 mg), and potassium carbonate (138 mg) were dissolved in acetonitrile (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0560] This intermediate, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (89 mg, yield 62%).

¹H-NMR (CDCl₃, 400 MHz): 1.42 - 1.55 (m, 2H), 2.03 - 2.12 (m, 2H), 2.30 - 2.40 (m, 2H), 2.91 - 3.00 (m, 2H), 3.25 - 3.34 (m, 1H), 3.75 (s, 2H), 6.76 - 6.81 (m, 2H), 6.93 - 7.03 (m, 1H), 7.17 - 7.23 (m, 2H), 7.25 - 7.33 (m, 1H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 359 (M⁺+1)

20

Example 151: N-[1-(2-Chlorobenzyl)tetrahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine

[0561] (R)-(-)-3-Pyrrolidinol hydrochloride (77 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 2-chlorobenzyl chloride (112 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0562] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was then concentrated to give intermediate B.

[0563] This intermediate B and 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (54 mg, yield 41%).

¹H-NMR (CDCl₃, 400 MHz): 1.61 - 1.75 (m, 1H), 2.23 - 2.34 (m, 1H), 2.44 - 2.53 (m, 1H), 2.63 - 2.70 (m, 1H), 2.77 - 2.88 (m, 2H), 3.73 (s, 2H), 3.95 - 4.03 (m, 1H), 6.68 - 6.71 (m, 1H), 6.72 - 6.77 (m, 1H), 7.11 - 7.18 (m, 2H), 7.20 - 7.24 (m, 1H), 7.26 - 7.30 (m, 1H), 7.40 (d, J = 6.8 Hz, 1H), 7.82 (s, 1H)

Mass spectrum (ESI-MS, m/z): 327 (M⁺+1)

40

Example 152: N-[1-(3-Chlorobenzyl)tetrahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine

45

[0564] (R)-(-)-3-Pyrrolidinol hydrochloride (77 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution of 3-chlorobenzyl chloride (112 mg) in acetonitrile (1 ml) was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0565] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0566] This intermediate B and 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried

55

over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (94 mg, yield 72%).

¹H-NMR (CDCl₃, 400 MHz): 1.68 - 1.79 (m, 1H), 2.30 - 2.41 (m, 1H), 2.42 - 2.51 (m, 1H), 2.61 - 2.67 (m, 1H), 2.76 - 2.86 (m, 2H), 3.62 (s, 2H), 4.01 - 4.08 (m, 1H), 6.74 - 6.77 (m, 1H), 6.79 - 6.83 (m, 1H), 7.18 - 7.26 (m, 3H), 7.29 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.89 (s, 1H)

Mass spectrum (ESI-MS, m/z): 327 (M⁺+1)

Example 153: N-[1-(4-Chlorobenzyl)tetrahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine

[0567] (R)-(-)-3-Pyrrolidinol hydrochloride (77 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-chlorobenzyl chloride (112 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0568] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0569] This intermediate B and 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (88 mg, yield 67%).

¹H-NMR (CDCl₃, 400 MHz): 1.67 - 1.77 (m, 1H), 2.30 - 2.41 (m, 1H), 2.41 - 2.50 (m, 1H), 2.59 - 2.65 (m, 1H), 2.75 - 2.85 (m, 2H), 3.61 (s, 2H), 4.00 - 4.07 (m, 1H), 6.73 - 6.76 (m, 1H), 6.77 - 6.82 (m, 1H), 7.24 - 7.30 (m, 5H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 327 (M⁺+1)

Example 154: N-[1-(4-Fluorobenzyl)tetrahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine

[0570] (R)-(-)-3-Pyrrolidinol hydrochloride (77 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-fluorobenzyl chloride (100 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0571] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0572] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (55 mg, yield 44%).

¹H-NMR (CDCl₃, 400 MHz): 1.67 - 1.78 (m, 1H), 2.30 - 2.40 (m, 1H), 2.41 - 2.50 (m, 1H), 2.60 - 2.68 (m, 1H), 2.76 - 2.84 (m, 2H), 3.62 (s, 2H), 4.00 - 4.08 (m, 1H), 6.73 - 6.76 (m, 1H), 6.76 - 6.81 (m, 1H), 6.96 - 7.03 (m, 3H), 7.26 - 7.32 (m, 2H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 311 (M⁺+1)

Example 155: N-[1-(4-Bromobenzyl)tetrahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine

[0573] (R)-(-)-3-Pyrrolidinol hydrochloride (96 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-bromobenzyl bromide (175 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0574] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a

sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0575] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (88 mg, yield 59%).

¹H-NMR (CDCl₃, 400 MHz): 1.60 - 1.70 (m, 1H), 2.23 - 2.33 (m, 1H), 2.33 - 2.42 (m, 1H), 2.52 - 2.58 (m, 1H), 2.67 - 2.78 (m, 2H), 3.53 (s, 3H), 3.92 - 4.00 (m, 1H), 6.66 - 6.69 (m, 1H), 6.70 - 6.75 (m, 1H), 7.14 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 371, 373 (M⁺, M⁺⁺²)

Example 156: N-(1H-5-Indazolyl)-N-[1-(4-methoxybenzyl)-tetrahydro-1H-3-pyrrolyl]amine

[0576] (R)-(-)-3-Pyrrolidinol hydrochloride (96 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-methoxybenzyl chloride (109 mg) in acetonitrile was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0577] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0578] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (56 mg, yield 44%).

¹H-NMR (CDCl₃, 400 MHz): 1.64 - 1.75 (m, 1H), 2.27 - 2.38 (m, 1H), 2.40 - 2.49 (m, 1H), 2.58 - 2.63 (m, 1H), 2.74 - 2.88 (m, 2H), 3.58 (s, 2H), 3.77 (s, 3H), 3.97 - 4.05 (m, 1H), 6.70 - 6.73 (m, 1H), 6.75 - 6.78 (m, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.20 - 7.26 (m, 3H), 7.85 (s, 1H)

Mass spectrum (ESI-MS, m/z): 323 (M⁺⁺¹)

Example 157: N-(1H-5-Indazolyl)-N-[1-(4-methylbenzyl)-tetrahydro-1H-3-pyrrolyl]amine

[0579] (R)-(-)-3-Pyrrolidinol hydrochloride (96 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-methylbenzyl chloride (98 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0580] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0581] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (56 mg, yield 40%).

¹H-NMR (CDCl₃, 400 MHz): 1.64 - 1.76 (m, 1H), 2.30 - 2.38 (m, 1H), 2.31 (s, 3H), 2.41 - 2.50 (m, 1H), 2.58 - 2.65 (m, 1H), 2.75 - 2.85 (m, 2H), 3.56 - 3.65 (m, 2H), 3.95 - 4.05 (m, 1H), 6.71 - 6.73 (m, 1H), 6.74 - 6.79 (m, 1H), 7.10 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 7.23 - 7.28 (m, 1H), 7.86 (s, 1H)

Mass spectrum (ESI-MS, m/z): 307 (M⁺⁺¹)

Example 158: N-(1H-5-Indazolyl)-N-[1-(3-nitrobenzyl)-tetrahydro-1H-3-pyrrolyl]amine

[0582] (R)-(-)-3-Pyrrolidinol hydrochloride (96 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-nitrobenzyl chloride (120 mg) in acetonitrile was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0583] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0584] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (81 mg, yield 60%).

¹H-NMR (CDCl₃, 400 MHz): 1.63 - 1.74 (m, 1H), 2.26 - 2.36 (m, 1H), 2.37 - 2.46 (m, 1H), 2.55 - 2.63 (m, 1H), 2.69 - 2.84 (m, 2H), 3.67 (s, 2H), 3.96 - 4.03 (m, 1H), 6.68 - 6.71 (m, 1H), 6.73 - 6.78 (m, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.82 (s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 8.16 (s, 1H)

Mass spectrum (ESI-MS, m/z): 338 (M⁺+1)

Example 159: N-(1H-5-Indazolyl)-N-[1-(4-nitrobenzyl)-tetrahydro-1H-3-pyrrolyl]amine

[0585] (R)-(-)-3-Pyrrolidinol hydrochloride (96 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-nitrobenzyl chloride (120 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0586] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0587] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (80 mg, yield 60%).

¹H-NMR (CDCl₃, 400 MHz): 1.55 - 1.75 (m, 1H), 2.26 - 2.36 (m, 1H), 2.36 - 2.48 (m, 1H), 2.50 - 2.63 (m, 1H), 2.70 - 2.85 (m, 2H), 3.65 - 3.71 (m, 2H), 3.95 - 4.04 (m, 1H), 6.67 - 6.70 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.41 - 7.28 (m, 2H), 7.81 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H)

Mass spectrum (ESI-MS, m/z): 338 (M⁺+1)

Example 160: N-[1-(3,5-Dimethoxybenzyl)tetrahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine

[0588] (R)-(-)-3-Pyrrolidinol hydrochloride (96 mg) and potassium carbonate (268 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3,5-dimethoxybenzyl chloride (130 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0589] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0590] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then

added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (72 mg, yield 51%).

¹H-NMR (CDCl₃, 400 MHz): 1.67 - 1.77 (m, 1H), 2.28 - 2.39 (m, 1H), 2.42 - 2.51 (m, 1H), 2.61 - 2.69 (m, 1H),

5 2.74 - 2.88 (m, 2H), 3.53 - 3.63 (m, 2H), 3.75 (s, 6H), 4.00 - 4.10 (m, 1H), 6.32 - 6.35 (m, 1H), 6.48 - 6.51 (m, 2H), 6.72
- 6.74 (m, 1H), 6.75 - 6.80 (m, 1H), 7.23 - 7.29 (m, 1H), 7.86 (s, 1H)

Mass spectrum (ESI-MS, m/z): 353 (M⁺+1)

Example 161: N-[1-(2-Chlorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0591] 3-Hydroxypiperidine (71 mg) and potassium carbonate (138 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 2-chlorobenzyl chloride (112 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0592] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0593] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (85 mg, yield 63%).

¹H-NMR (CDCl₃, 400 MHz): 1.42 - 1.74 (m, 4H), 2.31 - 2.53 (m, 3H), 2.65 - 2.75 (m, 1H), 3.51 - 3.60 (m, 3H), 6.71 - 6.79 (m, 2H), 7.07 - 7.18 (m, 2H), 7.21 (d, J = 8.8 Hz, 1H), 7.28 (dd, J = 1.7 Hz, 7.6 Hz, 1H), 7.34 - 7.42 (m, 1H), 7.78 (s, 1H)

Mass spectrum (ESI-MS, m/z): 341 (M⁺+1)

Example 162: N-[1-(3-Chlorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0594] 3-Hydroxypiperidine (71 mg) and potassium carbonate (138 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-chlorobenzyl chloride (112 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0595] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0596] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (63 mg, yield 46%).

¹H-NMR (CDCl₃, 400 MHz): 1.49 - 1.65 (m, 2H), 1.68 - 1.78 (m, 2H), 2.33 - 2.54 (m, 3H), 2.60 - 2.73 (m, 1H), 3.42 - 3.54 (m, 2H), 3.54 - 3.64 (m, 1H), 6.78 - 6.86 (m, 2H), 7.16 - 7.22 (m, 3H), 7.27 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.85 (s, 1H)

Mass spectrum (ESI-MS, m/z): 341 (M⁺+1)

Example 163: N-[1-(4-Chlorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0597] 3-Hydroxypiperidine (71 mg) and potassium carbonate (138 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-chlorobenzyl chloride (113 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0598] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0599] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (39 mg, yield 29%).

¹H-NMR (CDCl₃, 400 MHz): 1.43 - 1.57 (m, 2H), 1.62 - 1.74 (m, 2H), 2.20 - 2.40 (m, 3H), 2.63 - 2.70 (m, 1H), 3.33 - 3.48 (m, 2H), 3.48 - 3.58 (m, 1H), 6.72 - 6.78 (m, 2H), 7.18 - 7.24 (m, 5H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 341 (M⁺+1)

Example 164: N-[1-(4-Fluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0600] 3-Hydroxypiperidine (71 mg) and potassium carbonate (113 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-fluorobenzyl chloride (100 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0601] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0602] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (20 mg, yield 15%).

¹H-NMR (CDCl₃, 400 MHz): 1.43 - 1.58 (m, 2H), 1.60 - 1.75 (m, 2H), 2.20 - 2.40 (m, 3H), 2.61 - 2.75 (m, 1H), 3.34 - 3.47 (m, 2H), 3.47 - 3.58 (m, 1H), 6.72 - 6.78 (m, 2H), 6.89 - 6.96 (m, 2H), 7.19 - 7.25 (m, 3H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 325 (M⁺+1)

Example 165: N-[1-(4-Bromobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0603] 3-Hydroxypiperidine (71 mg) and potassium carbonate (113 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-bromobenzyl bromide (174 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0604] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0605] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (62 mg, yield 40%).

¹H-NMR (CDCl₃, 400 MHz): 1.42 - 1.57 (m, 2H), 1.60 - 1.73 (m, 2H), 2.20 - 2.38 (m, 3H), 2.60 - 2.75 (m, 1H), 3.33 - 3.47 (m, 2H), 3.48 - 3.57 (m, 1H), 6.71 - 6.78 (m, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.80 (s, 1H)

Mass spectrum (ESI-MS, m/z): 385, 387 (M⁺, M⁺+2)

Example 166: N-(1H-5-Indazolyl)-N-[1-(4-methoxybenzyl)-3-piperidyl]amine

[0606] 3-Hydroxypiperidine (71 mg) and potassium carbonate (113 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-methoxybenzyl chloride (109 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0607] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0608] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (25 mg, yield 19%).

¹H-NMR (CDCl₃, 400 MHz): 1.43 - 1.56 (m, 2H), 1.60 - 1.73 (m, 2H), 2.23 - 2.40 (m, 3H), 2.61 - 2.80 (m, 1H), 3.33 - 3.47 (m, 2H), 3.48 - 3.58 (m, 1H), 3.72 (s, 3H), 6.74 (s, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 337 (M⁺+1)

Example 167: N-(1H-5-Indazolyl)-N-[1-(4-methylbenzyl)-3-piperidyl]amine

[0609] 3-Hydroxypiperidine (71 mg) and potassium carbonate (113 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-methylbenzyl chloride (98 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0610] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0611] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (28 mg, yield 22%).

¹H-NMR (CDCl₃, 400 MHz): 1.42 - 1.57 (m, 2H), 1.60 - 1.72 (m, 2H), 2.26 (s, 3H), 2.24 - 2.39 (m, 3H), 2.62 - 2.75 (m, 1H), 3.35 - 3.48 (m, 2H), 3.48 - 3.58 (m, 1H), 6.71 - 6.78 (m, 2H), 7.05 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 321 (M⁺+1)

Example 168: N-(1H-5-Indazolyl)-N-[1-(3-nitrobenzyl)-3-piperidyl]amine

[0612] 3-Hydroxypiperidine (71 mg) and potassium carbonate (113 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-nitrobenzyl chloride (120 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0613] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0614] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then

added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (60 mg, yield 43%).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.52 - 1.66 (m, 2H), 1.71 - 1.84 (m, 2H), 2.26 - 2.50 (m, 3H), 2.70 - 2.80 (m, 1H),

3.52 - 3.65 (m, 3H), 6.77 - 6.85 (m, 2H), 7.27 (d, J = 8.8 Hz, 1H), 7.44 (dd, J = 7.8 Hz, 8.1 Hz, 1H), 7.63 (d, J = 6.8 Hz, 1H), 7.83 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 8.23 (s, 1H)

Mass spectrum (ESI-MS, m/z): 352 (M⁺+1)

Example 169: N-(1H-5-Indazolyl)-N-[1-(4-nitrobenzyl)-3-piperidyl]amine

¹⁰ [0615] 3-Hydroxypiperidine (71 mg) and potassium carbonate (113 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-nitrobenzyl chloride (120 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

¹⁵ [0616] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

²⁰ [0617] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (35 mg, yield 25%).

²⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.51 - 1.68 (m, 2H), 1.69 - 1.86 (m, 2H), 2.26 - 2.47 (m, 3H), 2.71 - 2.83 (m, 1H), 3.52 - 3.65 (m, 3H), 6.79 - 6.83 (m, 2H), 7.28 (d, J = 9.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.84 (s, 1H), 8.15 (d, J = 8.8 Hz, 2H)

Mass spectrum (ESI-MS, m/z): 352 (M⁺+1)

Example 170: N-[1-(3,5-Dimethoxybenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

³⁰ [0618] 3-Hydroxypiperidine (71 mg) and potassium carbonate (113 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3,5-dimethoxybenzyl chloride (130 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

³⁵ [0619] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (1 ml), and a sulfur trioxide-trimethylamine complex (209 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

⁴⁰ [0620] This intermediate B, 5-aminoindazole (53 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (55 mg, yield 38%).

⁴⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.40 - 1.57 (m, 2H), 1.62 - 1.75 (m, 2H), 2.20 - 2.43 (m, 3H), 2.70 - 2.80 (m, 1H), 3.35 - 3.47 (m, 2H), 3.50 - 3.60 (m, 1H), 3.73 (s, 6H), 6.29 (s, 1H), 6.45 (s, 2H), 6.72 - 6.79 (m, 2H), 7.22 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 367 (M⁺+1)

Example 171: N1-Benzyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

⁵⁵ [0621] 1,4-Cyclohexanedione monoethylene ketal (3.90 g), 5-aminoindazole (2.66 g), and acetic acid (0.5 ml) were dissolved in methanol (50 ml), and a borane-pyridine complex (2.50 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (50 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The

organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give intermediate A (4.09 g, yield 75%).

[0622] Intermediate A was dissolved in acetic acid-water (1 : 1, 50 ml), and the mixture was then stirred at 80°C for 3 hr. The reaction mixture was concentrated to remove a major part of acetic acid. A saturated aqueous sodium hydrogencarbonate solution was then added to the residue, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give intermediate B (3.21 g, yield 93%).

[0623] This intermediate B (115 mg), benzylamine (64 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by preparative TLC [chloroform/methanol] to give the title compound as a mixture of two diastereoisomers (1 : 1) (43 mg, yield 13%).

[0624] $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) (mixture of two diastereoisomers): 1.08 - 1.22 (m, 2H), 1.32 - 1.46 (m, 2H), 1.64 - 1.92 (m, 8H), 2.05 - 2.14 (m, 2H), 2.17 - 2.25 (m, 2H), 2.56 - 2.67 (m, 1H), 2.74 - 2.83 (m, 1H), 3.22 - 3.31 (m, 1H), 3.53 (m, 1H), 3.86 (s, 2H), 3.87 (s, 2H), 6.75 - 6.86 (m, 4H), 7.23 - 7.45 (m, 12H), 7.86 (s, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 321 ($\text{M}^{+}+1$)

Example 172: N1-(1H-5-Indazolyl)-N4-phenyl-1,4-cyclo-hexanediamine

[0625] 1,4-Cyclohexanedione monoethylene ketal (3.90 g), 5-aminoindazole (2.66 g), and acetic acid (0.5 ml) were dissolved in methanol (50 ml), and a borane-pyridine complex (2.50 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (50 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give intermediate A (4.09 g, yield 75%).

[0626] Intermediate A was dissolved in acetic acid-water (1 : 1, 50 ml), and the mixture was stirred at 80°C for 3 hr. The reaction mixture was concentrated to remove a major part of acetic acid. A saturated aqueous sodium hydrogencarbonate solution was then added to the residue, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give intermediate B (3.21 g, yield 93%).

[0627] This intermediate B (115 mg), aniline (56 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.06 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound as one diastereoisomer (12 mg, yield 8%).

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): 1.25 - 1.35 (m, 2H), 1.65 - 1.95 (m, 4H), 2.18 - 2.32 (m, 2H), 3.27 - 3.36 (m, 1H), 3.47 - 3.57 (m, 1H), 6.56 - 6.64 (m, 2H), 6.65 - 6.72 (m, 2H), 6.78 - 6.84 (m, 2H), 7.13 - 7.20 (m, 2H), 7.30 (d, $J = 9.0$ Hz, 1H), 7.89 (s, 1H)

Example 173: N1-(1H-5-Indazolyl)-2-(benzylamino)-acetamide

[0628] 2-[(Tert-butoxycarbonyl)amino]acetic acid (963 mg), 5-aminoindazole (665 mg), and dimethylaminopyridine (10 mg) were dissolved in dimethylformamide (20 ml). N-[3-(Diethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (1.54 g) and 1-hydroxybenzotriazole (1.22 g) were added to the solution at 0°C. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (20 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give intermediate A (849 mg, yield 59%).

[0629] Intermediate A was dissolved in chloroform (5 ml), and trifluoroacetic acid (5 ml) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 3 hr and was then concentrated to prepare intermediate B.

[0630] Intermediate B (546 mg), benzaldehyde (106 mg), and acetic acid (0.05 ml) were dissolved in methanol (2 ml), and sodium triacetoxyborohydride (212 mg) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (121 mg, yield 43%).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 3.46 (s, 2H), 3.86 (s, 2H), 7.25 - 7.46 (m, 7H), 8.02 (s, 1H), 8.10 (bs, 1H), 9.31 (bs, 1H)
Mass spectrum (ESI-MS, m/z): 281 (M⁺⁺)

¹⁰ Example 174: N1-Benzyl-N2-(1H-5-indazolyl)-1,2-ethane-diamine

[0631] N1-(1H-5-Indazolyl)-2-(benzylamino)acetamide (Example 173) (56 mg) was dissolved in tetrahydrofuran (1 ml), and a borane-tetrahydrofuran complex (1.0 ml) was added to the solution at room temperature. The reaction mixture was stirred at 50°C for 6 hr, and 1 N hydrochloric acid (0.5 ml) was then added, followed by stirring at the same temperature for one hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by preparative TLC [chloroform/methanol] to give the title compound (23 mg, yield 43%)

¹⁵ ¹H-NMR (CDCl₃, 400 MHz): 2.86 - 2.91 (m, 2H), 3.16 - 3.21 (m, 2H), 3.76 (s, 2H), 6.66 - 6.82 (m, 2H), 7.18 -
²⁰ 7.24 (m, 6H), 7.81 (s, 1H)
Mass spectrum (ESI-MS, m/z): 267 (M⁺⁺)

Example 175: N1-(1-Benzyl-4-piperidyl)-N1-(1H-5-indazolyl)acetamide

²⁵ Example 176: 1-[5-[(1-Benzyl-4-piperidyl)amino]-1H-5-indazolyl]-1-ethanone

[0632] N-(1-Benzyl-4-piperidyl)-N-(1H-5-indazolyl)amine (Example 126) (153 mg), triethylamine (0.14 ml), and dimethylaminopyridine (5 mg) were dissolved in chloroform (1 ml), and acetic anhydride (0.048 ml) was added dropwise to the solution at 0°C. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give a compound of Example 175 (11 mg, yield 6%) and a compound of Example 176 (40 mg, yield 23%).

³⁵ Example 175

[0633] ¹H-NMR (CDCl₃, 400 MHz): 1.23 - 1.40 (m, 1H), 1.50 - 1.70 (m, 1H), 1.70 - 1.80 (m, 1H), 1.82 - 1.92 (m, 1H),
2.02 (s, 3H), 2.11 - 2.29 (m, 2H), 2.11 - 2.29 (m, 2H), 2.91 - 3.08 (m, 2H), 3.48 (d, J = 12.7 Hz, 1H), 3.55 (d, J = 13.0
⁴⁰ Hz, 1H), 4.66 - 4.76 (m, 1H), 6.92 - 6.98 (m, 1H), 7.20 - 7.27 (m, 6H), 7.52 (s, 1H), 8.05 (s, 1H)
Mass spectrum (ESI-MS, m/z): 349 (M⁺⁺)

Example 176

[0634] ¹H-NMR (CDCl₃, 400 MHz): 1.50 - 1.62 (m, 2H), 2.05 - 2.13 (m, 2H), 2.18 - 2.28 (m, 2H), 2.73 (s, 3H), 2.85
⁴⁵ - 2.95 (m, 2H), 3.30 - 3.40 (m, 1H), 3.58 (s, 2H), 6.73 - 6.76 (m, 1H), 6.84 - 6.89 (m, 1H), 7.24 - 7.36 (m, 5H), 7.94 (s,
1H), 8.19 (d, J = 9.0 Hz, 1H)
Mass spectrum (ESI-MS, m/z): 349 (M⁺⁺)

Example 177: 1-Benzyl-4-piperidyl(1H-5-indazolyl)ether

[0635] 4-Amino-m-cresol (123 mg), potassium acetate (244 mg), and acetic anhydride (0.47 ml) were suspended in chlorobenzene (2 ml), and isoamyl nitrate (0.20 ml) was added to the suspension at 80°C. The reaction mixture was stirred at the same temperature for 18 hr, water (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give intermediate A.

[0636] Intermediate A was dissolved in hydrochloric acid-methanol (2 ml), and the mixture was then stirred at 80°C for 5 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and

the solvent was removed by distillation under the reduced pressure to give intermediate B.

[0637] This intermediate B, 1-benzyl-4-hydroxypiperidine (105 mg), and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and diethyl azodicarboxylate (0.20 ml) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (35 mg, yield 11%).

¹H-NMR (CDCl₃, 400 MHz): 1.71 - 1.84 (m, 2H), 1.92 - 2.00 (m, 2H), 2.20 - 2.30 (m, 2H), 2.65 - 2.75 (m, 2H), 3.48 (s, 2H), 4.16 - 4.28 (m, 2H), 6.96 - 7.03 (m, 1H), 7.07 - 7.09 (m, 1H), 7.20 - 7.28 (m, 5H), 7.30 (d, J = 9.0 Hz, 1H), 7.89 (s, 1H)

Mass spectrum (ESI-MS, m/z): 308 (M⁺+1)

Example 178: N1-(4-Pyridyl)-2-(2,4,6-trichlorophenoxy)-acetamide

[0638] 4-Aminopyridine (266 mg, 1.96 mmol, 1.0 eq), WSC· HCl (451 mg, 2.35 mmol, 1.2 eq), and HOBr·H₂O (320 mg, 2.35 mmol, 1.2 eq) were added to a solution of the carboxyl compound (500 mg, 1.96 mmol) prepared in Example 16 in dimethylformamide, and the mixture was stirred at room temperature for 16 hr.

[0639] After the completion of the reaction, the reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (276 mg, 42.6%).

MS m/z: 330, 332

¹H-NMR δ: 4.69 (2H, s), 7.67 (2H, dd, J = 1.59, 4.76 Hz), 7.70 (2H, s), 8.46 (2H, dd, J = 1.59, 4.76), 10.51 (1H, s)

Intermediate 1: 1H-5-Indazolol

[0640] 4-Amino-m-cresol (12.3 g), potassium acetate (24.4 g), and acetic anhydride (47.1 ml) were suspended in chlorobenzene (200 ml), and isoamyl nitrate (0.20 ml) was added to the suspension at 80°C. The reaction mixture was stirred at the same temperature for 18 hr. Water (100 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give intermediate A.

[0641] Intermediate A was dissolved in hydrochloric acid-methanol (200 ml), and the mixture was then stirred at 80°C for 5 hr. A saturated aqueous sodium hydrogencarbonate solution (200 ml) was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give the title compound (7.99 g).

¹H-NMR (CDCl₃, 400 MHz): 6.95 (d, J = 8.8 Hz, 1H), 7.03 (s, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.88 (s, 1H)

Intermediate 2: 1H-5-Indazolecarboxylic acid

[0642] Methyl 4-amino-3-methylbenzoate (0.85 g), potassium acetate (1.47 mg), and acetic anhydride (1.42 ml) were suspended in chlorobenzene (20 ml), and isoamyl nitrate (1.17 g) was added to the suspension at 80°C. The reaction mixture was stirred at the same temperature for 18 hr. Water (20 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in hydrochloric acid-methanol (20 ml), and the mixture was then stirred at 80°C for 5 hr. A saturated aqueous sodium hydrogencarbonate solution (20 ml) was added to the reaction mixture, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel [chloroform/methanol] to give intermediate A.

[0643] Intermediate A was dissolved in methanol (20 ml), and a 3 N aqueous sodium hydroxide solution (3 ml) was added thereto. The reaction mixture was stirred at room temperature for 18 hr. The solvent was then removed by distillation under the reduced pressure, and the residue was purified by ODS chromatography [water/acetonitrile] to give the title compound (0.32 g).

Mass spectrum (ESI-MS, m/z): 161 (M⁺-1)

Example 179: Tert-butyl (1H-5-indazolylamino)-1-pyrrolidinecarboxylate

[0644] (R)-(-)-3-Pyrrolidinol hydrochloride (1.23 g) was dissolved in a 3 N aqueous sodium hydroxide solution (10

ml), and a solution (10 ml) of di-tert-butyl dicarbonate (2.40 g) in THF was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for one hr and was then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate A.

[0645] This intermediate A and triethylamine (2 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (4.44 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0646] This intermediate B, 5-aminoindazole (0.98 g), and acetic acid (0.2 ml) were dissolved in methanol (10 ml), and a borane-pyridine complex (1.0 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel [chloroform/methanol] to give the title compound (1.59 g).

¹H-NMR (CDCl₃, 400 MHz): 1.44 (s, 9H), 1.68 - 1.78 (m, 1H), 1.96 - 2.06 (m, 1H), 2.85 - 3.00 (m, 1H), 3.03 - 3.20 (m, 1H), 3.35 - 3.43 (m, 1H), 3.65 - 3.75 (m, 1H), 3.98 - 4.20 (m, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.87 (s, 1H), 7.30 (d, J = 9.0 Hz, 1H), 7.86 (s, 1H)

Example 180: Tert-butyl 3-(1H-indazolylamino)-1-piperidinecarboxylate

[0647] 3-Hydroxypiperidine (1.01 g) was dissolved in a 3 N aqueous sodium hydroxide solution (10 ml), and a solution (10 ml) of di-tert-butyl dicarbonate (2.40 g) in THF was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for one hr and was then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate A.

[0648] This intermediate A and triethylamine (2 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (4.44 g) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0649] This intermediate B, 5-aminoindazole (0.98 g), and acetic acid (0.2 ml) were dissolved in methanol (10 ml), and a borane-pyridine complex (1 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel [chloroform/methanol] to give the title compound (2.30 g).

¹H-NMR (CDCl₃, 400 MHz): 1.44 (s, 9H), 1.83 - 2.02 (m, 3H), 2.15 - 2.25 (m, 1H), 3.30 - 3.56 (m, 4H), 3.98 - 4.10 (m, 1H), 4.40 - 4.46 (m, 1H), 6.77 - 6.81 (m, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H)

Intermediate 3: 4-(1H-5-Indazolylamino)-1-cyclohexanone

[0650] 1,4-Cyclohexanedione monoethylene ketal (3.90 g), 5-aminoindazole (2.66 g), and acetic acid (0.5 ml) were dissolved in methanol (50 ml), and a borane-pyridine complex (2.50 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr, was then cooled to room temperature, and was concentrated. The residue was dissolved in acetic acid-water (1 : 1, 50 ml), and the mixture was then stirred at 80°C for 3 hr. The reaction mixture was concentrated to remove a major part of acetic acid. A saturated aqueous sodium hydrogencarbonate solution was then added to the residue, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (3.21 g).

¹H-NMR (CDCl₃, 400 MHz): 1.70 - 1.84 (m, 2H), 2.31 - 2.54 (m, 6H), 3.72 - 3.84 (m, 1H), 6.83 (d, J = 8.83 Hz, 1H), 6.87 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.89 (s, 1H)

Intermediate 4: 4-(5-Isoquinolylamino)-1-cyclohexanone

[0651] 1,4-Cyclohexanedione monoethylene ketal (6.2 g), 5-amino-isoquinoline (4.3 g), and acetic acid (0.5 ml) were dissolved in methanol (50 ml), and a borane-pyridine complex (4.0 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr, was then cooled to room temperature, and was concentrated. The residue was dissolved in acetic acid-water (1 : 1, 50 ml), and the mixture was then stirred

at 80°C for 3 hr. The reaction mixture was concentrated to remove a major part of acetic acid. A saturated aqueous sodium hydrogencarbonate solution was then added to the residue, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (5.8 g).

¹H-NMR (CDCl₃, 400 MHz): 1.83 - 1.96 (m, 2H), 2.40 - 2.60 (m, 6H), 3.90 - 4.00 (m, 1H), 4.22 - 4.31 (m, 1H), 6.85 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.53 (d, J = 6.1 Hz, 1H), 8.47 (d, J = 6.1 Hz, 1H), 9.16 (s, 1H)

10 Example 181: N-(1H-5-Indazolyl)-N-(4-piperidyl)amine

[0652] Example 179 (450 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hr and was then concentrated to give the title compound (420 mg).

15 Mass spectrum (ESI-MS, m/z): 203 (M⁺+1)

Example 182: N-(1H-5-Indazolyl)-N-tetrahydro-1H-3-pyrrolylamine

[0653] Example 180 (474 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hr and was then concentrated to give the title compound (510 mg).

Mass spectrum (ESI-MS, m/z): 217 (M⁺+1)

25 Example 183: N-[1-(Cyclohexylmethyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0654] 4-Piperidone hydrochloride monohydrate (77 mg) and cyclohexanecarboxyaldehyde (62 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (106 mg) was added to the solution. The reaction mixture was stirred at room temperature for 18 hr. Further, 5-aminoindazole (54 mg) was added thereto, and the mixture was stirred for 30 min. A borane-pyridine complex (0.05 ml) was added thereto. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (15 mg).

¹H-NMR (CDCl₃, 400 MHz): 0.80 - 0.90 (m, 2H), 1.10 - 1.30 (m, 2H), 1.30 - 1.59 (m, 3H), 1.60 - 1.80 (m, 6H), 2.03 - 2.20 (m, 6H), 2.80 - 2.90 (m, 2H), 3.25 - 3.35 (m, 1H), 6.75 - 6.82 (m, 2H), 7.28 (d, J = 8.8 Hz, 1H), 7.86 (s, 1H)

Mass spectrum (ESI-MS, m/z): 313 (M⁺+1)

Example 184: N-(1H-5-Indazolyl)-N-(1-pentyl-4-piperidyl)amine

[0655] 4-Piperidone hydrochloride monohydrate (77 mg) and valeraldehyde (43 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (106 mg) was added to the solution. The reaction mixture was stirred at room temperature for 18 hr. Further, 5-aminoindazole (54 mg) was added thereto. The mixture was stirred for 30 min, and a borane-pyridine complex (0.05 ml) was added thereto. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (2 mg).

Mass spectrum (ESI-MS, m/z): 287 (M⁺+1)

50 Example 185: N-(1-Hexyl-4-piperidyl)-N-(1H-5-indazolyl)-amine

[0656] 4-Piperidone hydrochloride monohydrate (77 mg) and capronaldehyde (50 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (106 mg) was added to the solution. The reaction mixture was stirred at room temperature for 18 hr. Further, 5-aminoindazole (54 mg) was added thereto, and the mixture was stirred for 30 min, followed by the addition of a borane-pyridine complex (0.05 ml). The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/meth-

anol] to give the title compound (2 mg).

Mass spectrum (ESI-MS, m/z): 301 (M⁺+1)

Example 186: N-(1H-5-Indazolyl)-N-(1-isobutyl-4-piperidyl)amine

[0657] 4-Piperidone hydrochloride monohydrate (77 mg) and isobutylaldehyde (36 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (106 mg) was added thereto. The reaction mixture was stirred at room temperature for 18 hr. 5-Aminoindazole (54 mg) was further added thereto, and the mixture was stirred for 30 min, and a borane-pyridine complex (0.05 ml) was then added thereto. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (1 mg).

Mass spectrum (ESI-MS, m/z): 272 (M⁺+1)

Example 187: N-(1H-5-Indazolyl)-N-[1-(2-phenylpropyl)-4-piperidyl]amine

[0658] 4-Piperidone hydrochloride monohydrate (77 mg) and 2-phenylpropionaldehyde (68 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (106 mg) was added to the solution. The reaction mixture was stirred at room temperature for 18 hr. 5-Aminoindazole (54 mg) was further added thereto, and the mixture was stirred for 30 min, followed by the addition of borane-pyridine complex (0.05 ml). The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (21 mg).

Mass spectrum (ESI-MS, m/z): 335 (M⁺+1)

Example 188: N-[1-(2-Cyclohexenyl)methyl]-N-(1H-5-indazolyl)amine

[0659] 4-Piperidone hydrochloride monohydrate (77 mg) and 1,2,3,6-tetrahydrobenzaldehyde (55 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (106 mg) was added to the solution. The reaction mixture was stirred at room temperature for 18 hr. Further, 5-aminoindazole (54 mg) was added thereto, and the mixture was stirred for 30 min, followed by the addition of a borane-pyridine complex (0.05 ml). The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (6 mg).

Mass spectrum (ESI-MS, m/z): 301 (M⁺+1)

Example 189: (4-Benzylpiperazino)(1H-5-indazolyl)-methanone

[0660] 1-Benzylpiperazine (256 mg) and 1H-5-indazolecarboxylic acid (intermediate 2) (243 mg) were dissolved in dimethylformamide (3 ml), and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (263 mg), 1-hydroxybenzotriazole (225 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (30 mg).

¹H-NMR (CDCl₃, 400 MHz): 2.20 - 2.80 (m, 4H), 3.20 - 4.10 (m, 6H), 7.18 - 7.33 (m, 5H), 7.38 (d, J = 8.6 Hz,

50 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.78 (s, 1H), 8.04 (s, 1H)

Mass spectrum (ESI-MS, m/z): 321 (M⁺+1)

Example 190: N5-(1-Benzyltetrahydro-1H-3-pyrrolyl)-1H-5-indazolecarboxyamide

[0661] 1-Benzyl-3-aminopyrrolidine (256 mg) and 1H-5-indazolecarboxylic acid (intermediate 2) (243 mg) were dissolved in dimethylformamide (3 ml), and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (383 mg), 1-hydroxybenzotriazole (306 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added

thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (21 mg).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.90 - 2.03 (m, 1H), 2.37 - 2.57 (m, 2H), 2.73 - 2.83 (m, 1H), 3.02 - 3.12 (m, 1H), 3.20 - 3.32 (m, 1H), 3.83 (s, 2H), 4.79 - 4.89 (m, 1H), 7.23 - 7.40 (m, 6H), 7.81 (d, J = 8.8 Hz, 1H), 8.07 (s, 1H), 8.24 (s, 1H)
Mass spectrum (ESI-MS, m/z): 321 (M⁺+1)

Example 191: N5-(1-Benzyltetrahydro-1H-3-pyrrolyl)-1H-5-indazolecarboxyamide

¹⁰ [0662] 4-Amino-1-benzylpiperidine (280 mg) and 1H-5-indazolecarboxylic acid (intermediate 2) (243 mg) were dissolved in dimethylformamide (3 ml), and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (383 mg), 1-hydroxybenzotriazole (306 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (42 mg).

¹⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.60 - 1.80 (m, 2H), 1.95 - 2.08 (m, 2H), 2.20 - 2.32 (m, 2H), 2.90 - 2.98 (m, 2H), 3.07 (s, 2H), 3.80 - 3.86 (m, 1H), 7.16 - 7.40 (m, 5H), 7.46 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 8.07 (s, 1H), 8.14 (s, 1H)
²⁰ Mass spectrum (ESI-MS, m/z): 335 (M⁺+1)

Example 192: Ethyl 4-(1H-5-indazolylamino)-1-cyclohexanecarboxylate

²⁵ [0663] Ethyl 4-oxocyclohexanecarboxylate (0.85 g) and 5-aminoindazole (0.60 g) were dissolved in methanol (10 ml) thereto, and a borane-pyridine complex (0.81 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel [chloroform/methanol] to give the title compound (1.37 g) as substantially 1 : 1 enantiomers.

³⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.15 - 1.23 (m, 6H), 1.40 - 1.56 (m, 3H), 1.60 - 1.70 (m, 3H), 1.74 - 1.82 (m, 1H), 1.87 - 2.05 (m, 5H), 2.15 - 2.32 (m, 3H), 2.40 - 2.48 (m, 1H), 3.14 - 3.23 (m, 1H), 3.38 - 3.46 (m, 1H), 4.03 - 4.14 (m, 4H), 6.75 - 6.99 (m, 4H), 7.23 (d, J = 8.8 Hz, 2H), 7.81 (s, 1H), 7.83 (s, 1H)

Example 193: Ethyl 2-(1H-5-indazolylamino)-1-cyclohexanecarboxylate

³⁵ [0664] Ethyl 2-oxocyclohexanecarboxylate (0.85 g) and 5-aminoindazole (0.60 g) were dissolved in methanol (10 ml), and a borane-pyridine complex (0.81 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel [chloroform/methanol] to give the title compound (1.37 g) as substantially 1 : 1 enantiomers.

⁴⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.10 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 7.3 Hz, 3H), 1.33 - 1.46 (m, 4H), 1.55 - 1.75 (m, 5H), 1.80 - 1.88 (m, 1H), 1.90 - 1.99 (m, 2H), 2.10 - 2.20 (m, 1H), 2.25 - 2.37 (m, 1H), 2.78 - 2.88 (m, 2H), 3.49 (dt, J = 3.9 Hz, 10.5 Hz, 1H), 3.67 - 3.74 (m, 2H), 3.94 - 4.10 (m, 5H), 6.75 - 6.95 (m, 4H), 7.23 (d, J = 8.5 Hz, 2H), 7.81 (s, 2H)

Example 194: (3R)-1-Benzyltetrahydro-1H-3-pyrrolyl(1H-5-indazolyl)ether

⁴⁵ [0665] 1H-5-Indazolol (intermediate 1) (67 mg), (S)-1-benzyl-3-pyrrolidinol (89 mg), and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (42 mg).

⁵⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.94 - 2.02 (m, 1H), 2.21 - 2.33 (m, 1H), 2.48 - 2.63 (m, 1H), 2.65 - 2.77 (m, 2H), 2.90 - 3.00 (m, 1H), 3.60 (d, J = 12.7 Hz, 1H), 3.65 (d, J = 12.7 Hz, 1H), 4.73 - 4.84 (m, 1H), 6.92 (s, 1H), 6.97 (d, J =

9.0 Hz, 1H), 7.20 - 7.31 (m, 6H), 7.88 (s, 1H).

Example 195: (3S)-1-Benzyltetrahydro-1H-3-pyrrolyl(1H-5-indazolyl)ether

[0666] (R)-(-)-Pyrrolidinol hydrochloride (73 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of benzyl chloride (70 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0667] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (45 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.94 - 2.02 (m, 1H), 2.21 - 2.33 (m, 1H), 2.48 - 2.63 (m, 1H), 2.65 - 2.77 (m, 2H), 2.90 - 3.00 (m, 1H), 3.60 (d, J = 12.7 Hz, 1H), 3.65 (d, J = 12.7 Hz, 1H), 4.73 - 4.84 (m, 1H), 6.92 (s, 1H), 6.97 (d, J = 9.0 Hz, 1H), 7.20 - 7.31 (m, 6H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 294 (M⁺+1)

Example 196: 1-Benzyl-3-piperidyl(1H-5-indazolyl)ether

[0668] 3-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of benzyl chloride (70 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0669] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (46 mg).

Mass spectrum (ESI-MS, m/z): 308 (M⁺+1)

Example 197: 1H-5-Indazolyl(1-methyl-3-piperidyl)ether

[0670] 1H-5-Indazolol (intermediate 1) (67 mg), 1-methyl-3-hydroxypiperidine (58 mg), and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (36 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.50 (m, 1H), 1.50 - 1.65 (m, 1H), 1.75 - 1.90 (m, 1H), 1.90 - 2.05 (m, 1H), 2.05 - 2.25 (m, 2H), 2.25 (s, 3H), 2.50 - 2.60 (m, 1H), 2.85 - 2.95 (m, 1H), 4.26 - 4.36 (m, 1H), 7.02 (d, J = 9.0 Hz, 1H), 7.13 (s, 1H), 7.30 (d, J = 9.0 Hz, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 232 (M⁺+1)

Example 198: 1H-5-Indazolyl(1-methyl-3-piperidyl)ether

[0671] 1H-5-Indazolol (intermediate 1) (67 mg), 1-methyl-3-hydroxypiperidine (58 mg), and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (36 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.14 (t, J = 7.2 Hz, 3H), 1.70 - 1.90 (m, 3H), 1.96 - 2.05 (m, 1H), 2.21 - 2.36 (m, 1H), 2.38 - 2.50 (m, 1H), 2.80 - 2.91 (m, 1H), 2.93 - 3.05 (m, 1H), 3.15 - 3.25 (m, 1H), 3.85 (dd, J = 6.8 Hz, 9.0 Hz, 1H),

3.98 - 4.06 (m, 1H), 7.04 - 7.10 (m, 2H), 7.35 (d, J = 9.8 Hz, 1H), 7.94 (s, 1H)
 Mass spectrum (ESI-MS, m/z): 246 (M⁺+1)

Example 199: 1-(3-Cyclohexenylmethyl)-3-piperidyl(1H-5-indazoly)ether

[0672] 3-Hydroxypiperidine (71 mg) and 1,2,3,6-tetrahydrobenzaldehyde (77 mg) were dissolved in methanol/THF (1 : 1, 2 ml), and sodium triacetoxyborohydride (211 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give intermediate A.

[0673] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (20 mg).

Mass spectrum (ESI-MS, m/z): 312 (M⁺+1)

Example 200: 1-(2-Chlorobenzyl)-4-piperidyl(1H-5-indazoly)ether

[0674] 4-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 2-chlorobenzyl chloride (100 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0675] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (2 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.80 - 1.92 (m, 2H), 1.95 - 2.08 (m, 2H), 2.30 - 2.45 (m, 2H), 2.76 - 2.90 (m, 2H), 3.58 - 3.70 (m, 2H), 4.27 - 4.36 (m, 1H), 7.08 (d, J = 9.0 Hz, 1H), 7.14 (s, 1H), 7.24 - 7.28 (m, 3H), 7.33 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.94 (s, 1H)

Mass spectrum (ESI-MS, m/z): 342 (M⁺+1)

Example 201: 1-(3-Chlorobenzyl)-4-piperidyl(1H-5-indazoly)ether

[0676] 4-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-chlorobenzyl chloride (100 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0677] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (7 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.79 - 1.92 (m, 2H), 1.95 - 2.08 (m, 2H), 2.20 - 2.40 (m, 2H), 2.68 - 2.80 (m, 2H), 3.48 (s, 2H), 4.23 - 4.35 (m, 1H), 7.06 (d, J = 9.0 Hz, 1H), 7.14 (s, 1H), 7.18 - 7.28 (m, 3H), 7.34 (s, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.94 (s, 1H)

Mass spectrum (ESI-MS, m/z): 342 (M⁺+1)

Example 202: 1-(4-Chlorobenzyl)-4-piperidyl(1H-5-indazoly)ether

[0678] 4-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-chlorobenzyl chloride (100 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the

filtrate was concentrated to give intermediate A.

[0679] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (4 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.76 - 1.92 (m, 2H), 1.95 - 2.08 (m, 2H), 2.20 - 2.40 (m, 2H), 2.68 - 2.80 (m, 2H), 3.48 (s, 2H), 4.23 - 4.36 (m, 1H), 7.05 (d, J = 9.0 Hz, 1H), 7.13 (s, 1H), 7.24 - 7.28 (m, 4H), 7.36 (d, J = 9.0 Hz, 1H), 7.94 (s, 1H)

Mass spectrum (ESI-MS, m/z): 342 (M⁺⁺¹)

Example 203: 1-(4-Fluorobenzyl)-4-piperidyl(1H-5-indazolyl)ether

[0680] 4-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-fluorobenzyl chloride (86 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0681] 1H-5-Indazolo (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (7 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.72 - 1.85 (m, 2H), 1.88 - 2.03 (m, 2H), 2.15 - 2.33 (m, 2H), 2.60 - 2.75 (m, 2H), 3.44 (s, 2H), 4.20 - 4.30 (m, 1H), 6.88 - 6.97 (m, 2H), 7.01 (d, J = 9.0 Hz, 1H), 7.08 (s, 1H), 7.20 - 7.28 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 7.89 (s, 1H)

Mass spectrum (ESI-MS, m/z): 326 (M⁺⁺¹)

Example 204: 1H-5-Indazolyl[1-(3-nitrobenzyl)-4-piperidyl]ether

[0682] 4-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-nitrobenzyl chloride (103 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0683] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (11 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.80 - 1.92 (m, 2H), 1.95 - 2.08 (m, 2H), 2.28 - 2.40 (m, 2H), 2.68 - 2.80 (m, 2H), 3.61 (s, 2H), 4.28 - 4.38 (m, 1H), 7.07 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.49 (dd, J = 5.6 Hz, 7.8 Hz, 1H), 7.67 (d, J = 6.8 Hz, 1H), 7.95 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H)

Example 205: 1H-5-Indazolyl[1-(4-nitrobenzyl)-4-piperidyl]ether

[0684] 4-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-nitrobenzyl chloride (103 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0685] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (7 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.80 - 1.92 (m, 2H), 1.95 - 2.08 (m, 2H), 2.28 - 2.40 (m, 2H), 2.68 - 2.80 (m, 2H),

3.61 (s, 2H), 4.28 - 4.38 (m, 1H), 7.06 (d, J = 9.0 Hz, 1H), 7.14 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.95 (s, 1H), 8.16 (d, J = 8.8 Hz, 1H)

Mass spectrum (ESI-MS, m/z): 353 (M⁺+1)

5 Example 206: (3S)-1-(2-Chlorobenzyl)tetrahydro-1H-3-pyrrolyl(1H-5-indazolyl)ether

[0686] (R)-(-)-Pyrrolidinol hydrochloride (73 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 2-chlorobenzyl chloride (97 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0687] 1H-5-indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (25 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.95 - 2.08 (m, 1H), 2.33 (dt, J = 7.3 Hz, 14.2 Hz, 1H), 2.65 - 2.73 (m, 1H), 2.82 - 2.92 (m, 2H), 3.08 (dd, J = 6.1 Hz, 10.5 Hz, 1H), 3.82 (s, 2H), 4.80 - 4.88 (m, 1H), 6.99 (s, 1H), 7.02 (d, J = 9.0 Hz, 1H), 7.13 - 7.24 (m, 2H), 7.30 - 7.37 (m, 2H), 7.49 (d, J = 7.6 Hz, 1H), 7.95 (s, 1H)

20 Mass spectrum (ESI-MS, m/z): 328 (M⁺+1)

Example 207: (3S)-1-(3-Chlorobenzyl)tetrahydro-1H-3-pyrrolyl(1H-5-indazolyl)ether

[0688] (R)-(-)-Pyrrolidinol hydrochloride (73 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-chlorobenzyl chloride (97 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0689] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (25 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.92 - 2.08 (m, 1H), 2.33 (dt, J = 7.1 Hz, 13.9 Hz, 1H), 2.55 - 2.65 (m, 1H), 2.70 - 2.85 (m, 2H), 2.98 (dd, J = 6.1 Hz, 10.3 Hz, 1H), 3.63 (d, J = 13.2 Hz, 1H), 3.65 (d, J = 12.9 Hz, 1H), 4.80 - 4.88 (m, 1H), 6.97 (s, 1H), 7.02 (d, J = 9.0 Hz, 1H), 7.16 - 7.24 (m, 3H), 7.34 (d, J = 8.8 Hz, 1H), 7.33 - 7.37 (m, 1H), 7.95 (s, 1H)

Mass spectrum (ESI-MS, m/z): 328 (M⁺+1)

Example 208: (3S)-1-(4-Chlorobenzyl)tetrahydro-1H-3-pyrrolyl(1H-5-indazolyl)ether

[0690] (R)-(-)-Pyrrolidinol hydrochloride (73 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-chlorobenzyl chloride (97 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0691] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (14 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.95 - 2.08 (m, 1H), 2.29 (dt, J = 7.3 Hz, 13.9 Hz, 1H), 2.52 - 2.62 (m, 1H), 2.70 - 2.80 (m, 2H), 2.94 (dd, J = 6.3 Hz, 10.5 Hz, 1H), 3.60 (d, J = 13.2 Hz, 1H), 3.63 (d, J = 13.2 Hz, 1H), 4.77 - 4.84 (m, 1H), 6.94 (s, 1H), 7.02 (d, J = 9.0 Hz, 1H), 7.25 - 7.35 (m, 4H), 7.32 (d, J = 9.0 Hz, 1H), 7.91 (s, 1H)

55 Mass spectrum (ESI-MS, m/z): 328 (M⁺+1)

Example 209: (3S)-1-(4-Fluorobenzyl)tetrahydro-1H-3-pyrrolyl(1H-5-indazolyl)ether

[0692] (R)-(-)-Pyrrolidinol hydrochloride (73 mg) and potassium carbonate (165 mg) were dissolved in dimethylfor-

mamide (1 ml), and a solution (1 ml) of 4-fluorobenzyl chloride (97 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0693] 1H-5-Indazolo (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (18 mg).

¹⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.92 - 2.02 (m, 1H), 2.26 (dt, J = 6.8 Hz, 14.2 Hz, 1H), 2.48 - 2.57 (m, 1H), 2.65 - 2.77 (m, 2H), 2.90 (dd, J = 6.3 Hz, 10.5 Hz, 1H), 3.60 (d, J = 2.9 Hz, 1H), 3.59 (d, J = 12.9 Hz, 1H), 4.73 - 4.84 (m, 1H), 6.87 - 6.97 (m, 4H), 7.20 - 7.27 (m, 2H), 7.29 (d, J = 9.0 Hz, 1H), 7.91 (s, 1H)

Mass spectrum (ESI-MS, m/z): 312 (M⁺⁺1)

Example 210: (3S)-(1H-5-Indazolyl)[1-(3-nitrobenzyl)-tetrahydro-1H-3-pyrrolyl]ether

[0694] (R)-(-)-Pyrrolidinol hydrochloride (73 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-nitrobenzyl chloride (103 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0695] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (25 mg).

¹⁰ ¹H-NMR (CDCl₃, 400 MHz): 2.00 - 2.10 (m, 1H), 2.33 (dt, J = 7.3 Hz, 13.9 Hz, 1H), 2.55 - 2.65 (m, 1H), 2.75 - 2.86 (m, 2H), 2.98 (dd, J = 6.1 Hz, 10.5 Hz, 1H), 3.75 (d, J = 13.7 Hz, 1H), 3.76 (d, J = 13.4 Hz, 1H), 4.82 - 4.88 (m, 1H), 6.97 (s, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.08 (d, J = 6.8 Hz, 1H), 8.21 (s, 1H)

Example 211: (3S)-(1H-5-Indazolyl)[1-(4-nitrobenzyl)-tetrahydro-1H-3-pyrrolyl]ether

[0696] (R)-(-)-Pyrrolidinol hydrochloride (73 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-nitrobenzyl chloride (103 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0697] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (40 mg).

¹⁰ ¹H-NMR (CDCl₃, 400 MHz): 2.02 - 2.10 (m, 1H), 2.33 (dt, J = 7.6 Hz, 13.9 Hz, 1H), 2.55 - 2.63 (m, 1H), 2.75 - 2.86 (m, 2H), 2.98 (dd, J = 5.8 Hz, 10.2 Hz, 1H), 3.75 (d, J = 13.9 Hz, 1H), 3.76 (d, J = 13.9 Hz, 1H), 4.82 - 4.88 (m, 1H), 6.97 (s, 1H), 7.02 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.51 (t, J = 8.8 Hz, 2H), 7.93 (s, 1H), 8.15 (d, J = 8.8 Hz, 2H)

Mass spectrum (ESI-MS, m/z): 339 (M⁺⁺1)

Example 212: 1-(2-Chlorobenzyl)-3-piperidyl(1H-5-indazolyl)ether

[0698] 3-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 2-chlorobenzyl chloride (97 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0699] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-

carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (23 mg).

Mass spectrum (ESI-MS, m/z): 342 (M⁺+1)

5

Example 213: 1-(3-Chlorobenzyl)-3-piperidyl(1H-5-indazolyl)ether

[0700] 3-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-chlorobenzyl chloride (97 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0701] 1H-5-Indazolo (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (25 mg).

Mass spectrum (ESI-MS, m/z): 342 (M⁺+1)

20

Example 214: 1-(4-Chlorobenzyl)-3-piperidyl(1H-5-indazolyl)ether

[0702] 3-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-chlorobenzyl chloride (97 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0703] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (27 mg).

Mass spectrum (ESI-MS, m/z): 342 (M⁺+1)

35

Example 215: 1-(4-Fluorobenzyl)-3-piperidyl(1H-5-indazolyl)ether

[0704] 3-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 4-fluorobenzyl chloride (86 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0705] 1H-5-Indazolo (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (14 mg).

Mass spectrum (ESI-MS, m/z): 326 (M⁺+1)

45

Example 216: 1H-5-Indazolyl[1-(3-nitrobenzyl)-3-piperidyl]ether

[0706] 3-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3-nitrobenzyl chloride (103 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0707] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced

pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (25 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.57 (m, 1H), 1.57 - 1.70 (m, 1H), 1.73 - 1.88 (m, 1H), 2.05 - 2.15 (m, 1H), 2.15 - 2.34 (m, 2H), 2.63 - 2.68 (m, 1H), 2.304 (m, 2H), 3.63 (s, 1H), 4.32 - 4.38 (m, 1H), 7.05 (d, J = 9.0 Hz, 1H), 7.14 (s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 8.21 (s, 1H)

Example 217: 1H-5-Indazolyl[1-(1-phenylethyl)-3-piperidyl]ether

[0708] 3-Hydroxypiperidine (61 mg) and potassium carbonate (165 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of (1-bromoethyl)benzene (111 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0709] 1H-5-Indazolol (intermediate 1) (67 mg), intermediate A, and triphenylphosphine (131 mg) were dissolved in tetrahydrofuran (1 ml), and a solution (0.50 ml) of 40% diethyl azodicarboxylate in toluene was added thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (23 mg).

Mass spectrum (ESI-MS, m/z): 322 (M⁺+1)

Example 218: N-(1H-5-Indazolyl)-N-[1-(1-phenylethyl)-4-piperidyl]amine

[0710] 4-Piperidone hydrochloride monohydrate (77 mg) and potassium carbonate (138 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of (1-bromoethyl)benzene (93 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0711] This intermediate A, 5-aminoindazole (52 mg), and acetic acid (0.02 ml) were dissolved in methanol (1 ml), and a borane-pyridine complex (0.07 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (14 mg) as two diastereomers (ratio = ca. 50 : 50).

[0712] ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.40 - 1.75 (m, 10H), 1.98 - 2.28 (m, 8H), 2.80 - 2.95 (m, 2H), 3.00 - 3.15 (m, 2H), 3.20 - 3.32 (m, 2H), 3.50 - 3.63 (m, 2H), 6.73 - 6.78 (m, 4H), 7.23 - 7.28 (m, 6H), 7.30 - 7.34 (m, 6H), 7.84 (s, 2H)

Mass spectrum (ESI-MS, m/z): 321 (M⁺+1)

Example 219: N-(1H-5-Indazolyl)-N-[1-(1-phenylethyl)-tetrahydro-1H-3-pyrrolidyl]amine

[0713] The compound prepared in Example 179 (700 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hr and was then concentrated. Potassium carbonate (690 mg) and dimethylformamide (3 ml) were added to the concentrate, and the mixture was stirred. A solution (2 ml) of (1-bromoethyl)benzene (408 mg) in acetonitrile was added dropwise to the reaction solution, and the reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (3 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 150 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.30 - 1.39 (m, 6H), 1.54 - 1.72 (m, 1H), 2.17 - 2.28 (m, 2H), 2.28 - 2.45 (m, 3H), 2.53 - 2.61 (m, 1H), 2.65 - 2.70 (m, 2H), 2.70 - 2.77 (m, 2H), 3.17 - 3.25 (m, 2H), 3.88 - 3.98 (m, 2H), 6.63 - 6.73 (m, 4H), 7.10 - 7.30 (m, 12H), 7.80 (s, 1H), 7.82 (s, 1H)

Mass spectrum (ESI-MS, m/z): 307 (M⁺+1)

Example 220: N-(1H-5-Indazolyl)-N-[1-(1-phenylethyl)-3-piperidyl]amine

[0714] The compound prepared in Example 181 (700 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temper-

ature for 2 hr and was then concentrated. Potassium carbonate (690 mg) and dimethylformamide (3 ml) were added to the concentrate, and the mixture was stirred. A solution (2 ml) of (1-bromoethyl)benzene (408 mg) in acetonitrile was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (3 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 185 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

[0715] $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) as a mixture of 2 diastereomers: 1.28 - 1.34 (m, 6H), 1.40 - 1.55 (m, 4H), 1.55 - 1.70 (m, 4H), 2.18 - 2.45 (m, 3H), 2.64 - 2.74 (m, 2H), 3.41 - 3.54 (m, 4H), 6.66 - 6.78 (m, 4H), 7.12 - 7.26 (m, 12H), 7.80 (s, 2H)

Mass spectrum (ESI-MS, m/z): 321 (M⁺+1)

Example 221: Methyl 2-[3-(1H-5-indazolylamino)piperidino]-2-phenyl acetate

[0716] 3-Hydroxypiperidine (1.41 g) and potassium carbonate (2.76 g) were dissolved in dimethylformamide (20 ml), and a solution (20 ml) of methyl α -bromophenylacetate (3.23 g) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0717] This intermediate A and triethylamine (3 ml) were dissolved in anhydrous dimethyl sulfoxide (5 ml), and a sulfur trioxide-trimethylamine complex (3.69 g) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0718] This intermediate B, 5-aminoindazole (1.33 g), and acetic acid (0.2 ml) were dissolved in methanol (20 ml), and a borane-pyridine complex (1.5 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (20 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (3.55 g) as two diastereomers (ratio = ca. 50 : 50).

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) as a mixture of 2 diastereomers: 1.44 - 1.62 (m, 4H), 1.64 - 1.78 (m, 4H), 2.18 - 2.52 (m, 6H), 2.67 - 2.88 (m, 2H), 3.46 - 3.56 (m, 2H), 3.60 (s, 1H), 3.62 (s, 1H), 4.06 - 4.10 (m, 2H), 6.65 - 6.81 (m, 4H), 7.18 - 7.38 (m, 12H), 7.79 (s, 2H)

Mass spectrum (ESI-MS, m/z): 365 (M⁺+1)

Example 222: 2-[3-(1H-5-Indazolylamino)piperidino]-2-phenylacetic acid

[0719] The compound prepared in Example 221 (500 mg) was dissolved in methanol (1 ml) and a 3 N aqueous sodium hydroxide solution (1 ml) which was then stirred at room temperature for 18 hr. The reaction mixture was neutralized and adjusted to pH = about 7 by the addition of 1 N hydrochloric acid and was then concentrated.

[0720] The residue was purified by ODS column chromatography [water/acetonitrile] to give 450 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

Mass spectrum (ESI-MS, m/z): 349 (M⁺-1)

Example 223: N1-Methyl-2-[3-(1H-5-indazolylamino)-piperidino]-2-phenylacetamide

[0721] Methylamine (30 mg) and the compound prepared in Example 222 (88 mg) were dissolved in dimethylformamide (1 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (77 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 52 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) as a mixture of 2 diastereomers: 1.33 - 1.50 (m, 2H), 1.55 - 1.69 (m, 2H), 1.70 - 1.95 (m, 4H), 2.12 - 2.42 (m, 3H), 2.42 - 2.55 (m, 1H), 2.58 - 2.67 (m, 3H), 2.76 (s, 3H), 2.77 (s, 3H), 3.48 - 3.58 (m, 2H), 3.89 (s, 1H), 3.94 (s, 1H), 6.72 - 6.83 (m, 4H), 7.20 - 7.38 (m, 12H), 7.83 (s, 2H)

Mass spectrum (ESI-MS, m/z): 364 (M⁺+1)

Example 224: N1-Propyl-2-[3-(1H-5-indazolylamino)-piperidino]-2-phenylacetamide

[0722] Propylamine (30 mg) and the compound prepared in Example 222 (88 mg) were dissolved in dimethylformamide (1 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (77 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 72 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

¹⁰ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 0.79 (t, J = 7.3, 3H), 0.82 (t, J = 7.6, 3H), 1.25 - 1.50 (m, 6H), 1.52 - 1.65 (m, 2H), 1.65 - 1.78 (m, 2H), 1.78 - 1.94 (m, 2H), 2.00 - 2.20 (m, 2H), 2.22 - 2.33 (m, 1H), 2.40 - 2.55 (m, 2H), 2.70 - 2.87 (m, 3H), 2.90 - 3.03 (m, 1H), 3.10 - 3.19 (m, 4H), 3.45 - 3.54 (m, 2H), 3.83 (s, 1H), 3.86 (s, 1H), 6.65 - 6.76 (m, 4H), 7.15 - 7.27 (m, 12H), 7.78 (s, 2H)

Mass spectrum (ESI-MS, m/z): 391 (M⁺+1)

Example 225: N1-Cyclopropyl-2-[3-(1H-5-indazolylamino)-piperidino]-2-phenylacetamide

[0723] Cyclopropylamine (30 mg) and the compound prepared in Example 222 (88 mg) were dissolved in dimethylformamide (1 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (77 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 64 mg of the title compound as a single diastereomers.

²⁵ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: -0.50 - 0.06 (m, 4H), 0.16 - 0.34 (m, 4H), 1.10 - 1.23 (m, 2H), 1.23 - 1.35 (m, 2H), 1.40 - 1.50 (m, 2H), 1.55 - 1.75 (m, 3H), 1.80 - 1.90 (m, 1H), 1.98 - 2.10 (m, 2H), 2.12 - 2.18 (m, 1H), 2.18 - 2.28 (m, 1H), 2.30 - 2.39 (m, 1H), 2.40 - 2.50 (m, 1H), 3.00 - 3.10 (m, 2H), 3.40 (s, 1H), 3.41 (s, 1H), 6.25 - 6.35 (m, 4H), 6.75 - 6.87 (m, 12H), 7.39 (s, 1H), 7.40 (s, 1H)

Mass spectrum (ESI-MS, m/z): 390 (M⁺+1)

Example 226: N1,N1-Diethyl-2-[3-(1H-5-indazolylamino)-piperidino]-2-phenylacetamide

[0724] Diethylamine (35 mg) and the compound prepared in Example 222 (88 mg) were dissolved in dimethylformamide (1 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (77 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 58 mg of the title compound as a single diastereomers.

⁴⁰ ¹H-NMR (CDCl₃, 400 MHz) one diastereomer: 0.95 (t, J = 7.1, 3H), 1.01 (t, J = 7.1, 3H), 1.42 - 1.58 (m, 2H), 1.60 - 1.75 (m, 2H), 2.35 - 2.50 (m, 2H), 2.58 - 2.68 (m, 1H), 2.74 - 2.82 (m, 1H), 3.02 - 3.32 (m, 6H), 3.35 - 3.53 (m, 2H), 4.31 (s, 1H), 6.68 (s, 1H), 6.72 (t, J = 8.8, 1H), 7.15 - 7.30 (m, 4H), 7.30 - 7.37 (m, 2H), 7.76 (s, 2H)

Mass spectrum (ESI-MS, m/z): 406 (M⁺+1)

Example 227: N1-(2-Fluoroethyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide

[0725] 2-Fluoroethylamine hydrochloride (50 mg) and the compound prepared in Example 222 (88 mg) were dissolved in dimethylformamide (1 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (77 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 39 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

⁵⁵ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.27 - 1.40 (m, 2H), 1.55 - 1.68 (m, 2H), 1.68 - 1.80 (m, 2H), 1.80 - 1.92 (m, 2H), 1.95 - 2.15 (m, 2H), 2.24 - 2.35 (m, 2H), 2.45 - 2.60 (m, 2H), 2.75 - 2.85 (m, 2H), 3.25 - 3.45 (m, 2H), 3.45 - 3.62 (m, 2H), 3.90 (s, 2H), 4.27 - 4.40 (m, 2H), 4.40 - 4.55 (m, 2H), 6.67 - 6.73 (m, 4H), 7.15 - 7.30 (m, 12H), 7.79 (s, 1H), 7.80 (s, 1H)

Mass spectrum (ESI-MS, m/z): 396 (M⁺+1)

Example 228: N1,N1-Dimethyl-2-[3-(1H-5-indazolylamino)-piperidino]-2-phenylacetamide

[0726] Dimethylamine (100 mg) and the compound prepared in Example 222 (350 mg) were dissolved in dimethylformamide (5 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (257 mg), 1-hydroxybenzotriazole (227 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (5 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 180 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

[10] $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) as a mixture of 2 diastereomers: 1.40 - 1.60 (m, 4H), 1.60 - 1.77 (m, 4H), 2.22 - 2.52 (m, 4H), 2.52 - 2.65 (m, 2H), 2.70 - 3.03 (m, 2H), 2.86 (s, 6H), 3.44 - 3.54 (m, 4H), 4.32 - 4.45 (m, 2H), 6.65 - 6.79 (m, 4H), 7.15 - 7.40 (m, 12H), 7.75 - 7.80 (m, 2H)

Mass spectrum (ESI-MS, m/z): 378 ($M^{++}1$)

Example 229: Methyl 2-(4-fluorophenyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetate

[0727] Methyl 4-fluorophenylacetate (252 mg), N-bromosuccinimide (354 mg), and azobisisobutyronitrile (10 mg) were dissolved in carbon tetrachloride (3 ml), and the mixture was then stirred at 80°C for 18 hr. The reaction mixture was cooled to room temperature, and ether was then added thereto. The mixture was filtered through Celite and concentrated to give intermediate A.

[0728] The compound prepared in Example 180 (407 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hr and was then concentrated. Potassium carbonate (mg) and dimethylformamide (3 ml) were added to the concentrate, and the mixture was stirred. A solution of intermediate A in acetonitrile (2 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (3 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 370 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

[30] $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) as a mixture of 2 diastereomers: 1.52 - 1.70 (m, 4H), 1.70 - 1.90 (m, 4H), 2.32 - 2.64 (m, 6H), 2.75 - 2.95 (m, 2H), 3.55 - 3.65 (m, 2H), 3.65 (s, 3H), 3.66 (s, 3H), 4.12 - 4.28 (m, 2H), 6.90 - 7.04 (m, 8H), 7.34 - 7.48 (m, 6H), 7.83 (s, 2H)

Mass spectrum (ESI-MS, m/z): 383 ($M^{++}1$)

Example 230: Methyl 2-(4-chlorophenyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenyl acetate

[0729] Methyl 4-chlorophenylacetate (276 mg), N-bromosuccinimide (354 mg), and azobisisobutyronitrile (10 mg) were dissolved in carbon tetrachloride (3 ml), and the mixture was then stirred at 80°C for 18 hr. The reaction mixture was cooled to room temperature, and ether was then added thereto. The mixture was filtered through Celite and concentrated to give intermediate A.

[0730] The compound prepared in Example 180 (407 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hr and was then concentrated. Potassium carbonate (mg) and dimethylformamide (3 ml) were added to the concentrate, and the mixture was stirred. A solution of intermediate A in acetonitrile (2 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (3 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 420 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

[50] $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) as a mixture of 2 diastereomers: 1.52 - 1.70 (m, 4H), 1.68 - 1.90 (m, 4H), 2.32 - 2.60 (m, 6H), 2.75 - 2.93 (m, 2H), 3.53 - 3.65 (m, 2H), 3.65 (s, 3H), 3.66 (s, 3H), 4.10 - 4.22 (m, 2H), 6.80 - 6.97 (m, 4H), 7.22 - 7.40 (m, 12H), 7.84 (s, 2H)

Mass spectrum (ESI-MS, m/z): 399 ($M^{++}1$)

Example 231: N1-(2-Fluoroethyl)-2-(4-fluorophenyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide

[0731] The compound prepared in Example 229 (192 mg) was dissolved in methanol (1 ml) and a 3 N aqueous sodium hydroxide solution (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture

was neutralized and adjusted to pH = about 7 by the addition of 1 N hydrochloric acid and was then concentrated to give intermediate A.

[0732] 2-Fluoroethylamine hydrochloride (99 mg) and intermediate A were dissolved in dimethylformamide (2 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (191 mg), 1-hydroxybenzotriazole (153 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 111 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

¹⁰ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.25 - 1.42 (m, 2H), 1.45 - 1.67 (m, 2H), 1.68 - 1.77 (m, 2H), 1.80 - 1.92 (m, 2H), 2.00 - 2.20 (m, 2H), 2.24 - 2.35 (m, 2H), 2.40 - 2.55 (m, 2H), 2.70 - 2.80 (m, 2H), 3.25 - 3.63 (m, 6H), 3.89 (s, 1H), 3.92 (s, 1H), 4.27 - 4.38 (m, 2H), 4.40 - 4.55 (m, 2H), 6.63 - 6.77 (m, 4H), 6.85 - 6.97 (m, 4H), 7.10 - 7.25 (m, 4H), 7.50 - 7.65 (m, 2H), 7.79 (s, 1H), 7.80 (s, 1H)

Mass spectrum (ESI-MS, m/z): 414 (M⁺+1)

Example 232: N1-(2-Fluoroethyl)-2-(4-chlorophenyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide

[0733] The compound prepared in Example 230 (200 mg) was dissolved in methanol (1 ml) and a 3 N aqueous sodium hydroxide solution (1 ml). The solution was stirred at room temperature for 18 hr and was then neutralized and adjusted to pH = about 7 by the addition of 1 N hydrochloric acid, followed by concentration to give intermediate A.

[0734] 2-Fluoroethylamine hydrochloride (99 mg) and intermediate A were dissolved in dimethylformamide (2 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (191 mg), 1-hydroxybenzotriazole (153 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 109 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

¹⁰ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.25 - 1.40 (m, 2H), 1.50 - 1.67 (m, 2H), 1.68 - 1.77 (m, 2H), 1.77 - 1.92 (m, 2H), 2.00 - 2.20 (m, 2H), 2.24 - 2.35 (m, 2H), 2.40 - 2.57 (m, 2H), 2.70 - 2.90 (m, 2H), 3.25 - 3.65 (m, 6H), 3.89 (s, 1H), 3.92 (s, 1H), 4.27 - 4.40 (m, 2H), 4.40 - 4.55 (m, 2H), 6.63 - 6.77 (m, 4H), 7.10 - 7.25 (m, 10H), 7.50 - 7.70 (m, 2H), 7.79 (s, 1H), 7.80 (s, 1H)

Mass spectrum (ESI-MS, m/z): 430 (M⁺+1)

Example 233: N1-(O-Methylhydroxyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide

[0735] The compound prepared in Example 222 (175 mg) was dissolved in methanol (1 ml) and a 3 N aqueous sodium hydroxide solution (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was neutralized and adjusted to pH = about 7 by the addition of 1 N hydrochloric acid and was then concentrated to give intermediate A.

[0736] O-Methylhydroxylamine hydrochloride (84 mg) and intermediate A were dissolved in dimethylformamide (2 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (263 mg), 1-hydroxybenzotriazole (225 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 202 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

¹⁰ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.32 - 1.50 (m, 2H), 1.55 - 1.70 (m, 2H), 1.72 - 1.94 (m, 4H), 2.00 - 2.45 (m, 4H), 2.50 - 2.65 (m, 2H), 2.73 - 2.95 (m, 2H), 3.25 - 3.45 (m, 2H), 3.45 - 3.62 (m, 2H), 3.64 (s, 6H), 4.00 - 4.15 (m, 2H), 6.72 - 6.83 (m, 4H), 7.25 - 7.35 (m, 12H), 7.83 (s, 2H)

Example 234: N1-(O-Ethylhydroxyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide

[0737] The compound prepared in Example 222 (175 mg) was dissolved in methanol (1 ml) and a 3 N aqueous sodium hydroxide solution (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was neutralized and adjusted to pH = about 7 by the addition of 1 N hydrochloric acid and was then concentrated to give intermediate A.

[0738] O-Ethylhydroxylamine hydrochloride (98 mg) and intermediate A were dissolved in dimethylformamide (2 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (263 mg), 1-hydroxybenzotriazole (225 mg), and

dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 204 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

⁵ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.11 (t, J = 7.1, 6H), 1.30 - 1.45 (m, 2H), 1.55 - 1.65 (m, 2H), 1.68 - 1.88 (m, 4H), 2.15 - 2.40 (m, 4H), 2.45 - 2.60 (m, 2H), 2.73 - 2.85 (m, 2H), 3.45 - 3.55 (m, 2H), 3.70 - 3.88 (m, 4H), 3.96 - 4.15 (m, 2H), 6.70 - 6.77 (m, 4H), 7.20 - 7.27 (m, 12H), 7.78 (s, 2H)

¹⁰ Example 235: N1-(O-Methylhydroxyl)-N1-methyl-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide

[0739] The compound prepared in Example 222 (175 mg) was dissolved in methanol (1 ml) and a 3 N aqueous sodium hydroxide solution (1 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was neutralized and adjusted to pH = about 7 by the addition of 1 N hydrochloric acid and was then concentrated to give intermediate A.

[0740] N,O-Dimethylhydroxylamine hydrochloride (98 mg) and intermediate A were dissolved in dimethylformamide (2 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (263 mg), 1-hydroxybenzotriazole (225 mg), and dimethylaminopyridine (5 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 124 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

²⁰ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.45 - 2.05 (m, 8H), 2.33 - 3.05 (m, 8H), 3.15 (s, 6H), 3.42 (s, 6H), 3.55 - 3.73 (m, 2H), 4.76 (s, 1H), 4.87 (s, 1H), 6.76 - 6.85 (m, 4H), 7.23 - 7.38 (m, 8H), 7.38 - 7.48 (m, 4H), 7.79 (s, 2H)

Example 236: N-(1H-5-Indazolyl)-N-[1-(1-phenylpropyl)-3-piperidyl]amine

[0741] Ethylbenzene (110 mg), N-bromosuccinimide (267 mg), and azobisisobutyronitrile (10 mg) were dissolved in carbon tetrachloride (3 ml), and the mixture was then stirred at 80°C for 18 hr. The reaction mixture was cooled to room temperature, and ether was then added thereto. The mixture was filtered through Celite and was concentrated to give intermediate A.

[0742] The compound prepared in Example 180 (252 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hr and was then concentrated. Potassium carbonate (276 mg) and dimethylformamide (3 ml) were added to the concentrate, and the mixture was stirred. A solution of intermediate A in acetonitrile (2 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (3 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 130 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

³⁰ ³⁵ ⁴⁰ ⁴⁵ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 0.73 (q, J = 7.3 Hz, 6H), 1.35 - 1.90 (m, 8H), 2.20 - 2.75 (m, 2H), 2.20 - 2.45 (m, 4H), 3.20 - 3.30 (m, 2H), 3.38 - 3.58 (m, 2H), 6.66 - 6.76 (m, 4H), 7.07 - 7.27 (m, 12H), 7.80 (s, 2H)

Mass spectrum (ESI-MS, m/z): 335 (M⁺⁺1)

Example 237: N-(1H-5-Indazolyl)-N-[1-(1-phenylbutyl)-3-piperidyl]amine

[0743] Propylbenzene (120 mg), N-bromosuccinimide (267 mg), and azobisisobutyronitrile (10 mg) were dissolved in carbon tetrachloride (3 ml), and the mixture was then stirred at 80°C for 18 hr. The reaction mixture was cooled to room temperature, and ether was then added thereto. The mixture was filtered through Celite and was concentrated to give intermediate A.

[0744] The compound prepared in Example 180 (252 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hr and was then concentrated. Potassium carbonate (276 mg) and dimethylformamide (3 ml) were added to the concentrate, and the mixture was stirred. A solution of intermediate A in acetonitrile (2 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (3 ml) was then added thereto, and the mixture was extracted with chloroform-propanol

(3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 125 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

⁵ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 0.37 (q, J = 7.3 Hz, 6H), 0.60 - 0.85 (m, 4H), 0.85

- 1.46 (m, 8H), 1.70 - 2.00 (m, 6H), 2.05 - 2.40 (m, 2H), 2.85 - 2.97 (m, 2H), 2.97 - 3.15 (m, 2H), 6.25 - 6.33 (m, 4H), 6.65 - 6.85 (m, 12H), 7.38 (s, 2H)

Mass spectrum (ESI-MS, m/z): 349 (M⁺⁺)

Example 238: 2-[3-(1H-5-Indazolylamino)piperidino]-2-phenyl-1-ethanol

¹⁰ [0745] Lithium aluminum hydride (50 mg) was suspended in THF (2 ml), and a solution of Ki16245 (364 mg) in THF (2 ml) was added dropwise to the suspension at 0°C. The reaction mixture was stirred at room temperature for 18 hr and was then cooled to 0°C, and water (0.5 ml) was added dropwise to the cooled mixture. Sodium sulfate (300 mg) was added thereto, and the reaction mixture was stirred at room temperature for 3 hr and was then filtered through Celite. The solvent was removed from the filtrate by distillation under the reduced pressure, and the residue was purified by HPLC [chloroform/methanol] to give 293 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

¹⁵ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 1.40 - 1.80 (m, 8H), 2.40 - 2.55 (m, 2H), 2.55 - 2.75 (m, 2H), 2.75 - 3.05 (m, 2H), 3.40 - 3.80 (m, 6H), 3.90 - 4.10 (m, 2H), 6.71 - 6.79 (m, 4H), 7.15 - 7.35 (m, 12H), 7.80 (s, 2H)

Mass spectrum (ESI-MS, m/z): 337 (M⁺⁺)

Example 239: N1-(3,4-Dimethoxybenzyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide

²⁰ [0746] Veratrylamine (257 mg) and the compound prepared in Example 222 (350 mg) were dissolved in dimethylformamide (2 ml), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydro-chloride (256 mg), 1-hydroxybenzotriazole (227 mg), and dimethylaminopyridine (10 mg) were added to the solution. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give the title compound (310 mg).

³⁰ Mass spectrum (ESI-MS, m/z): 500 (M⁺⁺)

Example 240: N-(1H-5-Indazolyl)-N-[1-(2-methyl-1-phenylpropyl)-3-piperidy]amine

³⁵ [0747] Isobutylbenzene (201 mg), N-bromosuccinimide (354 mg), and azobisisobutyronitrile (10 mg) were dissolved in carbon tetrachloride (3 ml), and the mixture was then stirred at 80°C for 18 hr. The reaction mixture was cooled to room temperature, and ether was then added thereto. The mixture was filtered through Celite and was concentrated to give intermediate A.

⁴⁰ [0748] Example 180 (407 mg) was dissolved in chloroform (3 ml), and 95% trifluoroacetic acid (3 ml) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hr and was then concentrated. Potassium carbonate (414 mg) and dimethylformamide (3 ml) were added to the concentrate, and the mixture was stirred. A solution of intermediate A in acetonitrile (2 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (3 ml) was then added thereto, and the mixture was extracted with chloroform-propanol (3/1). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by HPLC [chloroform/methanol] to give 62 mg of the title compound as two diastereomers (ratio = ca. 50 : 50).

⁵⁰ ¹H-NMR (CDCl₃, 400 MHz) as a mixture of 2 diastereomers: 0.62 (d, J = 6.6 Hz, 3H), 0.63 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.0 Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H), 1.30 - 1.72 (m, 10H), 2.00 - 2.32 (m, 6H), 2.32 - 2.60 (m, 2H), 2.93 (d, J = 10.0 Hz, 1H), 2.96 (d, J = 11.2 Hz, 1H), 3.42 - 3.57 (m, 2H), 6.70 - 6.77 (m, 4H), 7.00 - 7.06 (m, 4H), 7.15 - 7.28 (m, 8H), 7.81 (s, 2H)

Mass spectrum (ESI-MS, m/z): 349 (M⁺⁺)

Example 241: N1-Benzyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

⁵⁵ [0749] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and benzylamine (53 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic

acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (14 mg) and a syn-form compound (24 mg).

5 (Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.05 - 1.32 (m, 4H), 1.95 - 2.03 (m, 2H), 2.05 - 2.20 (m, 2H), 2.52 (tt, J = 3.9 Hz, 11.0 Hz, 1H), 3.20 (tt, J = 3.7 Hz, 11.0 Hz, 1H), 3.70 (s, 2H), 6.68 - 6.77 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H), 7.25 - 7.30 (m, 5H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 321 (M⁺⁺¹)

10 (Syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.50 - 1.82 (m, 8H), 2.68 (tt, J = 3.9 Hz, 7.6 Hz, 1H), 3.44 - 3.52 (m, 1H), 3.90 (s, 2H), 6.70 - 6.77 (m, 2H), 7.20 - 7.32 (m, 6H), 7.80 (s, 1H)

Mass spectrum (ESI-MS, m/z): 321 (M⁺⁺¹)

15 Example 242: N1-(1H-5-Indazolyl)-N4-methyl-1,4-cyclohexanediamine

[0750] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and methylamine (20 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (1 mg) and a syn-form compound (1 mg).

25 (Anti form)

Mass spectrum (ESI-MS, m/z): 245 (M⁺⁺¹)

(Syn form)

Mass spectrum (ESI-MS, m/z): 245 (M⁺⁺¹)

30 Example 243: N1-(1H-5-Indazolyl)-N4-propyl-1,4-cyclohexanediamine

[0751] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and propylamine (30 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (5 mg) and a syn-form compound (5 mg).

40 (Anti form)

¹H-NMR (CDCl₃, 400 MHz): 0.87 (t, J = 7.3 Hz, 3H), 1.04 - 1.32 (m, 4H), 1.42 - 1.53 (m, 2H), 1.91 - 2.03 (m, 2H), 2.10 - 2.20 (m, 2H), 2.42 - 2.53 (m, 1H), 2.58 (t, J = 7.4 Hz, 2H), 3.19 (tt, J = 3.4 Hz, 10.5 Hz, 1H), 6.68 - 6.77 (m, 2H), 7.22 (d, J = 8.5 Hz, 1H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 273 (M⁺⁺¹)

45 (Syn form)

¹H-NMR (CDCl₃, 400 MHz): 0.87 (t, J = 7.4 Hz, 3H), 1.50 - 1.95 (m, 10H), 2.76 - 2.90 (m, 2H), 2.95 - 3.08 (m, 1H), 3.53 - 3.60 (m, 1H), 6.69 (s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.75 (s, 1H)

Mass spectrum (ESI-MS, m/z): 273 (M⁺⁺¹)

50 Example 244: N1-(1H-5-Indazolyl)-N4-(1-phenylethyl)-1,4-cyclohexanediamine

[0752] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and 1-phenylethylamine (61 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an

anti-form compound (20 mg) and a syn-form compound (15 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 0.90 - 1.30 (m, 4H), 1.30 (d, J = 2.6 Hz, 3H), 1.70 - 1.80 (m, 2H), 2.00 - 2.15 (m, 2H), 2.91 (tt, J = 3.7 Hz, 11.0 Hz, 2H), 3.14 (tt, J = 3.6 Hz, 10.7 Hz, 1H), 3.90 (s, 1H), 6.66 - 6.76 (m, 2H), 7.15 - 7.30 (m, 6H), 7.80 (s, 1H)

Mass spectrum (ESI-MS, m/z): 335 (M⁺⁺1)

(Syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.31 (d, J = 6.6 Hz, 3H), 1.48 - 1.78 (m, 8H), 2.40 - 2.50 (m, 1H), 3.40 - 3.48 (m, 1H), 3.85 - 3.92 (m, 1H), 6.70 - 6.77 (m, 2H), 7.15 - 7.30 (m, 6H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 335 (M⁺⁺1)

Example 245: N1-(4-Fluorobenzyl)-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

[0753] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and 4-fluorobenzylamine (70 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (20 mg) and a syn-form compound (12 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.01 - 1.30 (m, 4H), 1.92 - 2.04 (m, 2H), 2.08 - 2.18 (m, 2H), 2.49 (tt, J = 3.6 Hz, 10.7 Hz, 1H), 3.19 (tt, J = 3.7 Hz, 10.8 Hz, 1H), 3.74 (s, 2H), 6.68 - 6.76 (m, 2H), 6.94 (t, J = 8.8 Hz, 2H), 7.16 - 7.28 (m, 3H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 339 (M⁺⁺1)

(Syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.60 (m, 2H), 1.60 - 1.71 (m, 4H), 1.71 - 1.82 (m, 2H), 2.62 - 2.70 (m, 1H), 3.43 - 3.50 (m, 1H), 3.72 (s, 2H), 6.70 - 6.77 (m, 2H), 6.93 (t, J = 8.8 Hz, 2H), 7.16 - 7.28 (m, 3H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 339 (M⁺⁺1)

Example 246: N1-(2-Fluoroethyl)-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

[0754] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and 2-fluoroethylamine hydrochloride (50 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added to the reaction mixture, and the mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (12 mg) and a syn-form compound (12 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.00 - 1.40 (m, 4H), 1.91 - 2.00 (m, 2H), 2.10 - 2.20 (m, 2H), 2.49 (tt, J = 7.4 Hz, 10.7 Hz, 1H), 2.85 (t, J = 4.9 Hz, 1H), 2.92 (t, J = 4.9 Hz, 1H), 3.19 (tt, J = 3.7 Hz, 10.6 Hz, 1H), 4.43 (t, J = 4.8 Hz, 1H), 4.55 (t, J = 4.8 Hz, 1H), 6.68 - 6.77 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H), 7.82 (s, 1H)

Mass spectrum (ESI-MS, m/z): 277 (M⁺⁺1)

(syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.56 (m, 2H), 1.58 - 1.70 (m, 4H), 1.70 - 1.82 (m, 2H), 2.60 (m, 1H), 2.84 (t, J = 4.9 Hz, 1H), 2.91 (t, J = 4.9 Hz, 1H), 3.45 - 3.53 (m, 1H), 4.44 (t, J = 4.9 Hz, 1H), 4.56 (t, J = 4.9 Hz, 1H), 6.68 - 6.75 (m, 2H), 7.22 (d, J = 9.5 Hz, 1H), 7.80 (s, 1H)

Mass spectrum (ESI-MS, m/z): 277 (M⁺⁺1)

Example 247: N1-Cyclopropyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

[0755] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and cyclopropylamine (30 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5%

aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (5 mg) and a syn-form compound (12 mg).

5 (Anti form)

¹H-NMR (CDCl₃, 400 MHz): -0.13 - -0.07 (m, 2H), -0.03 - 0.02 (m, 2H), 0.65 - 0.85 (m, 4H), 1.60 - 1.75 (m, 5H), 2.12 - 2.21 (m, 1H), 2.72 - 2.81 (m, 1H), 6.28 - 6.33 (m, 2H), 6.80 (d, J = 8.6 Hz, 1H), 7.40 (s, 1H)

Mass spectrum (ESI-MS, m/z): 271 (M⁺⁺1)

10 (syn form)

¹H-NMR (CDCl₃, 400 MHz): -0.13 - -0.07 (m, 2H), -0.04 - 0.02 (m, 2H), 1.02 - 1.16 (m, 2H), 1.18 - 1.38 (m, 6H), 1.64 (tt, J = 3.7 Hz, 6.6 Hz, 1H), 2.28 - 2.38 (m, 1H), 3.04 - 3.10 (m, 1H), 6.28 - 6.35 (m, 2H), 6.80 (d, J = 9.5 Hz, 1H), 7.39 (s, 1H)

Mass spectrum (ESI-MS, m/z): 271 (M⁺⁺1)

15 Example 248: N1-(1H-5-Indazolyl)-1,4-cyclohexanediamine

[0756] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and ammonium acetate (100 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile] to give an anti-form compound (10 mg) and a syn-form compound (12 mg).

(Anti form)

Mass spectrum (ESI-MS, m/z): 231 (M⁺⁺1)

25 (syn form)

Mass spectrum (ESI-MS, m/z): 231 (M⁺⁺1)

Example 249: N1-Cyclohexylmethyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

[0757] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and cyclohexanemethylamine (57 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (29 mg) and a syn-form compound (35 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 0.78 - 0.92 (m, 2H), 1.06 - 1.28 (m, 7H), 1.30 - 1.45 (m, 1H), 1.55 - 1.80 (m, 5H), 1.90 - 2.00 (m, 2H), 2.10 - 2.20 (m, 2H), 2.38 - 2.51 (m, 3H), 3.15 - 3.25 (m, 1H), 6.71 - 6.77 (m, 2H), 7.22 (d, J = 8.3 Hz, 1H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 327 (M⁺⁺1)

(syn form)

¹H-NMR (CDCl₃, 400 MHz): 0.76 - 0.90 (m, 2H), 1.05 - 1.25 (m, 4H), 1.35 - 1.45 (m, 1H), 1.45 - 1.82 (m, 12H), 2.41 (d, J = 6.6 Hz, 1H), 2.56 (tt, J = 3.9 Hz, 8.3 Hz, 1H), 3.90 - 4.10 (m, 2H), 6.67 - 6.75 (m, 2H), 7.21 (d, J = 9.5 Hz, 1H), 7.80 (s, 1H)

Mass spectrum (ESI-MS, m/z): 327 (M⁺⁺1)

Example 250: N1-Cyclopropylmethyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

[0758] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and cyclopropylmethylamine (54 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (13 mg) and a syn-form compound (7 mg).

(Anti form)

Mass spectrum (ESI-MS, m/z): 285 (M⁺⁺1)

(Syn form)

- 5 ¹H-NMR (CDCl₃, 400 MHz): -0.09 - 0.04 (m, 2H), 0.30 - 0.40 (m, 2H), 0.82 - 0.88 (m, 2H), 1.42 - 1.80 (m, 8H),
 2.39 (d, J = 6.8 Hz, 2H), 2.55 - 2.63 (m, 1H), 3.40 - 3.50 (m, 1H), 6.62 - 6.68 (m, 2H), 7.12 (d, J = 9.8 Hz, 1H), 7.70 (s, 1H)
 Mass spectrum (ESI-MS, m/z): 285 (M⁺⁺1)

Example 251: N1-Cyclohexyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

- 10 [0759] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and cyclohexylamine (50 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (22 mg) and a syn-form compound (23 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.01 - 1.38 (m, 10H), 1.61 - 1.74 (m, 2H), 1.82 - 1.92 (m, 2H), 1.92 - 2.04 (m, 2H),

- 20 2.08 - 2.18 (m, 2H), 2.55 - 2.75 (m, 2H), 3.12 - 3.25 (m, 1H), 6.66 - 6.77 (m, 2H), 7.22 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H)
 Mass spectrum (ESI-MS, m/z): 313 (M⁺⁺1)

(Syn form)

- 25 ¹H-NMR (CDCl₃, 400 MHz): 1.02 - 1.25 (m, 4H), 1.35 - 1.58 (m, 4H), 1.58 - 1.75 (m, 2H), 1.77 - 2.10 (m, 8H),
 2.85 - 2.98 (m, 1H), 3.01 - 3.14 (m, 1H), 3.50 - 3.61 (m, 1H), 6.70 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.8
 Hz, 1H), 7.73 (s, 1H)

Mass spectrum (ESI-MS, m/z): 313 (M⁺⁺1)Example 252: N1-Cycloheptyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

- 30 [0760] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and cycloheptylamine (57 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (20 mg) and a syn-form compound (31 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.03 - 1.28 (m, 4H), 1.30 - 1.39 (m, 4H), 1.39 - 1.54 (m, 4H), 1.55 - 1.67 (m, 2H),

- 40 1.72 - 1.86 (m, 2H), 1.90 - 2.00 (m, 2H), 2.10 - 2.20 (m, 2H), 2.56 (tt, J = 3.6 Hz, 10.5 Hz, 1H), 2.70 - 2.82 (m, 1H),
 3.17 (tt, J = 3.6 Hz, 10.7 Hz, 1H), 6.67 - 6.75 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H)
 Mass spectrum (ESI-MS, m/z): 327 (M⁺⁺1)

(Syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.23 - 1.69 (m, 14H), 1.72 - 1.88 (m, 4H), 1.88 - 2.05 (m, 2H), 2.84 - 3.04 (m, 2H),

- 45 3.50 - 3.60 (m, 1H), 6.71 (s, 1H), 6.75 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 9.0 Hz, 1H), 7.75 (s, 1H)
 Mass spectrum (ESI-MS, m/z): 327 (M⁺⁺1)

Example 253: N1-(2,3-Dihydro-1H-indenyl)-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

- 50 [0761] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and 1-aminoindan (67 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (17 mg) and a syn-form compound (18 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.06 - 1.23 (m, 2H), 1.24 - 1.40 (m, 2H), 1.70 - 1.82 (m, 1H), 1.94 - 2.09 (m, 2H), 2.11 - 2.20 (m, 2H), 2.32 - 2.42 (m, 1H), 2.67 - 2.80 (m, 2H), 2.90 - 3.00 (m, 1H), 3.22 (tt, J = 3.9 Hz, 11.0 Hz, 1H), 4.31 (t, J = 6.6 Hz, 1H), 6.70 - 6.77 (m, 2H), 7.10 - 7.19 (m, 3H), 7.22 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 4.4 Hz, 1H), 7.81 (s, 1H)

5 Mass spectrum (ESI-MS, m/z): 347 (M⁺⁺)
(Syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.50 - 1.89 (m, 9H), 2.32 - 2.43 (m, 1H), 2.68 - 2.79 (m, 1H), 2.82 - 3.00 (m, 2H), 3.45 - 3.54 (m, 1H), 4.28 (t, J = 6.6 Hz, 1H), 6.71 - 6.77 (m, 2H), 7.08 - 7.15 (m, 3H), 7.19 (d, J = 9.5 Hz, 1H), 7.31 (d, J = 3.7 Hz, 1H), 7.80 (s, 1H)

10 Mass spectrum (ESI-MS, m/z): 347 (M⁺⁺)

Example 254: N1-(1H-5-Indazolyl)-N4-[(1S)-1,2,3,4-tetrahydro-1-naphthalenyl]-1,4-cyclohexanediamine

[0762] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and (S)-1,2,3,4-tetrahydro-1-naphthylamine (74 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (9 mg) and a syn-form compound (14 mg). (Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.08 - 1.38 (m, 4H), 1.57 - 1.95 (m, 5H), 2.04 - 2.21 (m, 3H), 2.58 - 2.70 (m, 3H), 3.22 (tt, J = 3.7 Hz, 10.7 Hz, 1H), 3.82 (t, J = 4.4 Hz, 1H), 6.71 - 6.77 (m, 2H), 6.97 - 7.04 (m, 1H), 7.04 - 7.25 (m, 2H), 7.22 (d, J = 8.6 Hz, 1H), 7.26 - 7.32 (m, 1H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 361 (M⁺⁺)

(Syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.52 - 2.04 (m, 12H), 2.64 (dt, J = 8.3 Hz, 16.8 Hz, 1H), 2.77 (dt, J = 5.4 Hz, 17.1 Hz, 1H), 2.86 - 2.95 (m, 1H), 3.45 - 3.54 (m, 1H), 3.78 - 3.93 (m, 1H), 6.75 (s, 1H), 6.78 (d, J = 8.8 Hz, 1H), 7.33 - 7.41 (m, 1H), 7.78 (s, 1H)

Mass spectrum (ESI-MS, m/z): 361 (M⁺⁺)

Example 255: N1-(1H-5-Indazolyl)-N4-(1,2,2-trimethylpropyl)-1,4-cyclohexanediamine

[0763] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and (2-amino-3,3-dimethylbutane (51 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (8 mg) and a syn-form compound (5 mg). (Anti form)

¹H-NMR (CDCl₃, 400 MHz): 0.89 (s, 9H), 1.01 - 1.20 (m, 5H), 1.93 - 2.21 (m, 3H), 2.26 - 2.75 (m, 1H), 3.15 - 3.25 (m, 1H), 6.66 - 6.75 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 315 (M⁺⁺)

(Syn form)

¹H-NMR (CDCl₃, 400 MHz): 0.85 (s, 9H), 0.91 - 1.05 (m, 3H), 1.40 - 1.83 (m, 8H), 2.20 - 2.37 (m, 1H), 2.57 - 2.75 (m, 1H), 3.38 - 3.50 (m, 1H), 6.73 (s, 1H), 6.76 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H)

50 Mass spectrum (ESI-MS, m/z): 315 (M⁺⁺)

Example 256: N1-(1H-5-Indazolyl)-N4-[1-(1H-3-Indolyl)ethyl]-1,4-cyclohexanediamine

[0764] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and tryptamine (80 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was

added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (26 mg) and a syn-form compound (24 mg).

(Anti form)

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.02 - 1.25 (m, 4H), 1.85 - 1.95 (m, 2H), 2.05 - 2.17 (m, 2H), 2.44 (tt, J = 3.9 Hz, 10.8 Hz, 1H), 2.86 - 2.97 (m, 4H), 3.16 (tt, J = 3.6 Hz, 10.8 Hz, 1H), 6.67 - 6.73 (m, 2H), 6.98 (s, 1H), 7.05 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 9.8 Hz, 1H), 7.29 (t, J = 8.1 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.81 (s, 1H), 8.02 (s, 1H)

Mass spectrum (ESI-MS, m/z): 374 (M⁺⁺1)

(Syn form)

¹⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.38 - 1.52 (m, 2H), 1.53 - 1.76 (m, 9H), 2.59 (tt, J = 3.9 Hz, 8.3 Hz, 1H), 2.93 (s, 1H), 3.43 - 3.51 (m, 1H), 6.65 - 6.73 (m, 2H), 6.97 (s, 1H), 7.05 (t, J = 8.1 Hz, 1H), 7.13 (t, J = 8.3 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.79 (s, 1H), 8.05 (s, 1H)

Mass spectrum (ESI-MS, m/z): 374 (M⁺⁺1)

15

Example 257: N1-[2-(1H-5-Imidazolyl)ethyl]-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

[0765] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and histamine hydrochloride (92 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (1 mg) and a syn-form compound (2 mg).

(Anti form)

Mass spectrum (ESI-MS, m/z): 374 (M⁺⁺1)

(Syn form)

Mass spectrum (ESI-MS, m/z): 374 (M⁺⁺1)

30

Example 258: N1-(1H-5-Indazolyl)-N4-[2-(3-thienyl)-ethyl]-1,4-cyclohexanediamine

[0766] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and 2-thiophenethylamine (64 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (30 mg) and a syn-form compound (23 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.05 - 1.28 (m, 4H), 1.90 - 2.00 (m, 2H), 2.08 - 2.20 (m, 2H), 2.46 (tt, J = 3.6 Hz, 10.5 Hz, 1H), 2.90 (t, J = 5.6 Hz, 2H), 2.96 (t, J = 8.0 Hz, 1H), 3.16 (tt, J = 3.7 Hz, 10.7 Hz, 1H), 6.67 - 6.75 (m, 2H), 6.77 (d, J = 3.4 Hz, 1H), 6.86 (dd, J = 3.4 Hz, 5.1 Hz, 1H), 7.07 (d, J = 5.1 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 341 (M⁺⁺1)

(Syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.42 - 1.54 (m, 2H), 1.58 - 1.78 (m, 6H), 2.64 (tt, J = 3.9 Hz, 8.0 Hz, 1H), 2.89 (t, J = 6.8 Hz, 1H), 2.99 (t, J = 6.4 Hz, 2H), (s, 1H), 3.43 - 3.51 (m, 1H), 6.67 - 6.74 (m, 2H), 6.75 - 6.78 (m, 1H), 6.83 - 6.88 (m, 1H), 7.07 (d, J = 5.1 Hz, 1H), 7.20 (d, J = 9.3 Hz, 1H), 7.79 (s, 1H)

50

Mass spectrum (ESI-MS, m/z): 341 (M⁺⁺1)

Example 259: N1-(1H-5-Indazolyl)-N4-phenylethyl-1,4-cyclohexanediamine

[0767] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and 2-phenethylamine (61 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was added thereto, and the mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then

added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (30 mg) and a syn-form compound (24 mg).

(Anti form)

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.02 - 1.25 (m, 4H), 1.88 - 1.96 (m, 2H), 2.07 - 2.16 (m, 2H), 2.45 (tt, J = 3.7 Hz, 10.5 Hz, 1H), 2.75 (t, J = 7.1 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 3.17 (tt, J = 3.7 Hz, 10.5 Hz, 1H), 6.67 - 6.75 (m, 2H), 7.10 - 7.17 (m, 3H), 7.17 - 7.25 (m, 3H), 7.81 (s, 1H)

Mass spectrum (ESI-MS, m/z): 335 (M⁺+1)

(Syn form)

¹⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.50 - 1.65 (m, 2H), 1.65 - 1.88 (m, 6H), 2.76 - 2.88 (m, 1H), 2.97 (s, 4H), 3.45 - 3.55 (m, 1H), 6.65 - 6.70 (m, 2H), 7.07 - 7.19 (m, 6H), 7.74 (s, 1H)

Mass spectrum (ESI-MS, m/z): 335 (M⁺+1)

Example 260: N1-(5-Isoquinolyl)-N4-propyl-1,4-cyclohexanediamine

¹⁵ [0768] 4-(5-Isoquinolylamino)-1-cyclohexanone (intermediate 4) (60 mg) and propylamine (30 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (18 mg) and a syn-form compound (22 mg).

(Anti form)

²⁵ ¹H-NMR (CDCl₃, 400 MHz): 0.87 (t, J = 7.4 Hz, 3H), 1.18 - 1.33 (m, 4H), 1.41 - 1.52 (m, 2H), 1.94 - 2.06 (m, 2H), 2.14 - 2.26 (m, 2H), 2.44 - 2.58 (m, 1H), 2.57 (t, J = 7.5 Hz, 2H), 3.31 - 3.44 (m, 1H), 4.06 - 4.20 (m, 1H), 6.70 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 6.1 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 9.07 (s, 1H)

Mass spectrum (ESI-MS, m/z): 284 (M⁺+1)

(Syn form)

³⁰ ¹H-NMR (CDCl₃, 400 MHz): 0.86 (t, J = 7.3 Hz, 3H), 1.40 - 1.50 (m, 2H), 1.50 - 1.60 (m, 2H), 1.68 - 1.76 (m, 4H), 1.80 - 1.90 (m, 2H), 2.57 (t, J = 7.3 Hz, 2H), 2.58 - 2.68 (m, 1H), 3.60 - 3.70 (m, 1H), 4.33 - 4.45 (m, 1H), 6.68 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 5.8 Hz, 1H), 8.37 (d, J = 6.1 Hz, 1H), 9.07 (s, 1H)

Mass spectrum (ESI-MS, m/z): 284 (M⁺+1)

Example 261: N1-(2-Fluoroethyl)-N4-(5-isooquinolyl)-1,4-cyclohexanediamine

[0769] 4-(5-Isoquinolylamino)-1-cyclohexanone (intermediate 4) (60 mg) and 2-fluoroethylamine hydrochloride (50 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC g [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (18 mg) and a syn-form compound (12 mg).

(Anti form)

⁴⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.18 - 1.34 (m, 4H), 1.95 - 2.05 (m, 2H), 2.16 - 2.30 (m, 2H), 2.45 - 2.60 (m, 1H), 2.86 (t, J = 4.9 Hz, 1H), 2.93 (t, J = 4.9 Hz, 1H), 3.33 - 3.45 (m, 1H), 4.07 - 4.21 (m, 1H), 4.44 (t, J = 4.8 Hz, 1H), 4.56 (t, J = 4.7 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 6.1 Hz, 1H), 8.38 (d, J = 6.1 Hz, 1H), 9.07 (s, 1H)

Mass spectrum (ESI-MS, m/z): 288 (M⁺+1)

(syn form)

⁵⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.50 - 1.62 (m, 2H), 1.63 - 1.78 (m, 4H), 1.80 - 1.90 (m, 2H), 2.69 (tt, J = 3.9 Hz, 7.8 Hz, 1H), 2.84 (t, J = 4.9 Hz, 1H), 2.91 (t, J = 4.7 Hz, 1H), 3.60 - 3.70 (m, 1H), 4.31 - 4.41 (m, 1H), 4.44 (t, J = 5.0 Hz, 1H), 4.56 (t, J = 5.0 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.46 (d, J = 6.1 Hz, 1H), 8.38 (d, J = 6.1 Hz, 1H), 9.07 (s, 1H)

Mass spectrum (ESI-MS, m/z): 284 (M⁺+1)

Example 262: N1-Cyclopropyl-N4-(5-isoquinolyl)-1,4-cyclohexanediamine

[0770] 4-(5-Isoquinolylamino)-1-cyclohexanone (intermediate 4) (60 mg) and cyclopropylamine (30 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (11 mg) and a syn-form compound (12 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): -0.16 - -0.09 (m, 2H), -0.04 - 0.20 (m, 2H), 0.75 - 0.93 (m, 4H), 1.58 - 1.72 (m, 3H), 1.75 - 1.85 (m, 2H), 2.16 - 2.27 (m, 1H), 2.87 - 3.03 (m, 1H), 3.60 - 3.85 (m, 1H), 6.29 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 7.00 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 6.0 Hz, 1H), 7.96 (d, J = 6.1 Hz, 1H), 8.65 (s, 1H)

Mass spectrum (ESI-MS, m/z): 282 (M⁺+1)

(Syn form)

¹H-NMR (CDCl₃, 400 MHz): -0.04 - 0.02 (m, 2H), 0.07 - 0.13 (m, 2H), 0.90 - 1.58 (m, 8H), 1.68 - 1.78 (m, 1H), 2.48 (tt, J = 3.9 Hz, 7.8 Hz, 1H), 3.28 - 3.40 (m, 1H), 3.95 - 4.13 (m, 1H), 6.39 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 7.16 (t, J = 6.1 Hz, 1H), 8.08 (d, J = 5.8 Hz, 1H), 8.76 (s, 1H)

Mass spectrum (ESI-MS, m/z): 282 (M⁺+1)Example 263: N1-(5-Isoquinolyl)-N4-phenylethyl-1,4-cyclohexanediamine

[0771] 4-(5-Isoquinolylamino)-1-cyclohexanone (intermediate 4) (60 mg) and 2-phenylethylamine (61 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile]. A saturated aqueous sodium hydrogencarbonate solution (2 ml) was then added to fractions containing respective compounds, followed by extraction with chloroform-propanol (3/1). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under the reduced pressure to give an anti-form compound (24 mg) and a syn-form compound (11 mg).

(Anti form)

¹H-NMR (CDCl₃, 400 MHz): 1.15 - 1.30 (m, 4H), 1.92 - 2.03 (m, 2H), 2.12 - 2.25 (m, 2H), 2.45 - 2.55 (m, 1H), 2.76 (t, J = 7.1 Hz, 2H), 2.88 (t, J = 7.1 Hz, 2H), 3.29 - 3.42 (m, 1H), 4.05 - 4.18 (m, 1H), 6.69 (d, J = 7.6 Hz, 1H), 7.12 - 7.26 (m, 6H), 7.37 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 6.1 Hz, 1H), 8.37 (d, J = 6.1 Hz, 1H), 9.06 (s, 1H)

Mass spectrum (ESI-MS, m/z): 346 (M⁺+1)

(syn form)

¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.58 (m, 2H), 1.64 - 1.74 (m, 4H), 1.76 - 1.86 (m, 2H), 2.65 (tt, J = 3.7 Hz, 8.1 Hz, 1H), 2.76 (tt, J = 6.8 Hz, 7.3 Hz, 2H), 2.86 (tt, J = 6.8 Hz, 7.1 Hz, 2H), 3.60 - 3.70 (m, 1H), 4.28 - 4.42 (m, 1H), 6.69 (d, J = 7.6 Hz, 1H), 7.10 - 7.26 (m, 6H), 7.37 (t, J = 7.9 Hz, 1H), 7.46 (d, J = 6.1 Hz, 1H), 8.38 (d, J = 6.1 Hz, 1H), 9.07 (s, 1H)

Mass spectrum (ESI-MS, m/z): 346 (M⁺+1)Example 264: N1-(1H-5-Indazolyl)-N4-isopropyl-1,4-cyclohexanediamine

[0772] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and 2-thiophenethylamine (64 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile] to give an anti-form compound (21 mg) and a syn-form compound (14 mg).

(Anti form)

Mass spectrum (ESI-MS, m/z): 273 (M⁺+1)

(Syn form)

Mass spectrum (ESI-MS, m/z): 273 (M⁺+1)

Example 265: N1-(1H-5-Indazolyl)-N4-isobutyl-1,4-cyclohexanediamine

[0773] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and isobutylamine (37 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile] to give an anti-form compound (8 mg) and a syn-form compound (6 mg).

(Anti form)

Mass spectrum (ESI-MS, m/z): 287 (M⁺⁺¹)

(Syn form)

Mass spectrum (ESI-MS, m/z): 287 (M⁺⁺¹)

Example 266: N1-Ethyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine

[0774] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and ethylamine (23 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile] to give an anti-form compound (10 mg) and a syn-form compound (10 mg).

(Anti form)

Mass spectrum (ESI-MS, m/z): 259 (M⁺⁺¹)

(Syn form)

Mass spectrum (ESI-MS, m/z): 259 (M⁺⁺¹)

Example 267: N1-(1H-5-Indazolyl)-N4-pentyl-1,4-cyclohexanediamine

[0775] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and amylamine (44 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile] to give an anti-form compound (10 mg) and a syn-form compound (10 mg).

(Anti form)

Mass spectrum (ESI-MS, m/z): 301 (M⁺⁺¹)

(Syn form)

Mass spectrum (ESI-MS, m/z): 301 (M⁺⁺¹)

Example 268: N1-(1H-5-Indazolyl)-N4-pentyl-1,4-cyclohexanediamine

[0776] 4-(1H-5-Indazolylamino)-1-cyclohexanone (intermediate 3) (57 mg) and N-phenylethylenediamine (68 mg) were dissolved in methanol (1 ml), and sodium triacetoxyborohydride (105 mg) was added by portions to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. Hydrochloric acid-methanol was then added thereto, and the reaction mixture was stirred and was then concentrated. The residue was purified by HPLC [0.5% aqueous trifluoroacetic acid solution/acetonitrile] to give an anti-form compound (51 mg) and a syn-form compound (45 mg).

(Anti form)

Mass spectrum (ESI-MS, m/z): 350 (M⁺⁺¹)

(Syn form)

Mass spectrum (ESI-MS, m/z): 350 (M⁺⁺¹)

Example 269: N-(5-Isoquinolyl)-N-[1-(4-methylpentyl)-3-piperidyl]amine

[0777] 3-Hydroxypiperidine (1 g) and potassium carbonate (2.76 g) were dissolved in anhydrous N,N-dimethylformamide (10 ml), and 1-bromo-4-methylpentane (1.65 g) was added dropwise to the solution at room temperature. The reaction solution was stirred at room temperature for 18 hr. Ethyl acetate was then added thereto, and the mixture was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The organic layer was concen-

trated under the reduced pressure to give an intermediate.

[0778] This intermediate and triethylamine (2.01 g) were dissolved in anhydrous dimethyl sulfoxide (10.2 ml), and a sulfur trioxide-trimethylamine complex (2.78 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (7.55 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated under the reduced pressure to give 1.52 g of an intermediate as a crude compound.

[0779] This intermediate (760 mg) and 5-aminoisoquinoline (473 mg) were dissolved in titanium tetraisopropoxide (3.8 ml), and the mixture was then stirred at room temperature for 18 hr. Methanol (3.8 ml) and sodium borohydride (77.6 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (17.4 mg, yield 1.36%).

¹H-NMR (CDCl₃, 400 MHz): 0.91 (dd, J = 2.0, 6.6 Hz, 6H), 1.22 - 1.28 (m, 2H), 1.48 - 1.61 (m, 4H), 1.73 - 1.78

(m, 2H), 2.29 - 2.41 (m, 4H), 2.47 - 2.59 (m, 1H), 2.66 - 2.75 (m, 1H), 3.74 - 3.84 (m, 1H), 6.77 (d, J = 7.6 Hz, 1H), 7.5 (d, J = 6.6 Hz, 1H), 7.27 (s, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 5.9 Hz, 1H), 8.45 (d, J = 6.1 Hz, 1H)

Mass spectrum (ESI-MS, m/z): 312 (M⁺+1)

Example 270: N-(1H-5-Indazolyl)-N-[1-(4-methylpentyl)-3-piperidyl]amine

[0780] The above intermediate (760 mg) and 5-aminoindazole (437 mg) were dissolved in titanium tetraisopropoxide (3.8 ml), and the mixture was then stirred at room temperature for 18 hr. Methanol (3.8 ml) and sodium borohydride (77.6 mg) were added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with 40 ml of ethyl acetate, and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (8.0 mg, yield 0.53%).

¹H-NMR (CDCl₃, 400 MHz): 0.88 (d, J = 6.6 Hz, 6H), 1.14 - 1.20 (m, 2H), 1.45 - 1.59 (m, 1H), 1.72 - 1.83 (m, 2H), 2.27 - 2.35 (m, 4H), 2.45 - 2.55 (m, 1H), 2.72 - 2.82 (m, 1H), 3.54 - 3.66 (m, 1H), 6.82 - 6.85 (m, 2H), 7.28 - 7.30 (m, 1H), 7.87 (s, 1H)

Mass spectrum (ESI-MS, m/z): 301 (M⁺+1)

Example 271: N-(1H-5-Indazolyl)-N-[1-(4-methylpentyl)-4-piperidyl]amine

[0781] 4-Piperidone hydrochloride monohydrate (768 mg) and potassium carbonate (1.38 g) were dissolved in anhydrous N,N-dimethylformamide (10 ml), and 1-bromo-4-methylpentane (603 mg) was added dropwise to the solution at room temperature. The reaction solution was stirred at room temperature for 18 hr. Ethyl acetate was then added thereto, and the mixture was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The organic layer was concentrated under the reduced pressure to give an intermediate.

[0782] This intermediate (766 mg) was dissolved in titanium tetraisopropoxide (3.8 ml). 5-Aminoindazole (445 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol (3.8 ml) and sodium borohydride (79 mg) were added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (200 mg, yield 13.3%).

¹H-NMR (CDCl₃, 400 MHz): 0.89 (d, J = 6.6 Hz, 6H), 1.15 - 1.26 (m, 2H), 1.49 - 1.59 (m, 5H), 2.07 - 2.23 (m, 1H), 2.35 - 2.39 (m, 2H), 2.90 - 3.00 (m, 2H), 3.29 - 3.38 (m, 1H), 6.80 - 6.82 (m, 2H), 7.26 (s, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 301 (M⁺+1), 299 (M⁺-1)

Example 272: N-(1H-5-Indazolyl)-N-[1-(4,4,4-trifluorobutyl)-3-piperidyl]amine

[0783] 3-Hydroxypiperidine (1 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and 1-bromo-4,4,4-trifluorobutane (1.91 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.

[0784] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (7.55 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer

was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.

[0785] This intermediate (800 mg) and 5-aminoindazole (403 mg) were dissolved in titanium tetrakisopropoxide (3.2 g), and the mixture was then stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (71 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (125 mg, yield 3.83%).

¹H-NMR (CDCl₃, 400 MHz): 1.56 - 1.58 (m, 1H), 1.70 - 1.78 (m, 5H), 2.09 - 2.21 (m, 2H), 2.37 - 2.42 (m, 5H), 2.70 - 2.80 (m, 1H), 3.54 - 3.64 (m, 1H), 6.81 - 6.85 (m, 2H), 7.29 - 7.32 (m, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 327 (M⁺+1), 325 (M⁺-1)

Example 273: N-(5-Isoquinolyl)-N-[1-(4,4,4-trifluorobutyl)-3-piperidyl]amine

[0786] The above intermediate (800 mg) and 5-aminoisoquinoline (433 mg) were dissolved in titanium tetrakisopropoxide (3.2 g), and the mixture was then stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (71 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (263 mg, yield 1.56%).

¹H-NMR (CDCl₃, 400 MHz): 1.60 - 1.83 (m, 8H), 2.42 - 2.52 (m, 2H), 3.75 - 3.84 (m, 1H), 4.85 - 5.00 (m, 1H), 6.76 - 6.78 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.52 (d, J = 6.1 Hz, 1H), 8.46 (d, J = 6.1 Hz, 1H)

Mass spectrum (ESI-MS, m/z): 338 (M⁺+1), 336 (M⁺-1)

Example 274: N-(1H-5-Indazolyl)-N-(1-isopentyl-3-piperidyl)amine

[0787] 3-Hydroxypiperidine (1 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and 1-chloro-3-methylbutane (1.07 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.

[0788] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (7.55 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.

[0789] This intermediate (775 mg) and 5-aminoindazole (482 mg) were dissolved in titanium tetrakisopropoxide (3.8 g), and the mixture was then stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (85 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (105 mg, yield 3.67%).

¹H-NMR (CDCl₃, 400 MHz): 0.89 - 0.91 (m, 6H), 1.35 - 1.41 (m, 3H), 1.54 - 1.76 (m, 6H), 2.32 - 2.37 (m, 3H), 2.45 - 2.50 (m, 1H), 3.55 - 3.63 (m, 1H), 6.82 - 6.97 (m, 2H), 7.28 - 7.32 (m, 1H), 7.87 - 7.88 (m, 1H)

Mass spectrum (ESI-MS, m/z): 278 (M⁺+1)

Example 275: N-(1-Isopentyl-3-piperidyl)-N-(5-isoquinolyl)amine

[0790] The above intermediate (775 mg) and 5-aminoisoquinoline (523 mg) were dissolved in titanium tetrakisopropoxide (3.8 g), and the mixture was then stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (85 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (145 mg, yield 4.87%).

¹H-NMR (CDCl₃, 400 MHz): 0.94 (dd, J = 4.6, 6.6 Hz, 6H), 1.39 - 1.45 (m, 2H), 1.51 - 1.73 (m, 6H), 2.36 - 2.70 (m, 5H), 4.21 (m, 1H), 6.94 - 6.98 (m, 1H), 7.25 - 7.27 (m, 1H), 7.38 - 7.46 (m, 1H), 7.52 - 7.58 (m, 1H), 8.44 - 8.50 (m, 1H), 9.13 - 9.18 (m, 1H)

Mass spectrum (ESI-MS, m/z): 297 (M⁺+1)

Example 276: N-(5-Isoquinolyl)-N-[1-(2,4,6-trifluorobenzyl)-3-piperidyl]amine

- 5 [0791] 3-Hydroxypiperidine (1 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and 2,4,6-trifluorobenzyl bromide (2.25 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.
- 10 [0792] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (7.55 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.
- 15 [0793] This intermediate (766 mg) was dissolved in titanium tetraisopropoxide (2.3 g). 5-Aminoisoquinoline (304 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol (2.8 ml) and sodium borohydride (50 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (172 mg, yield 4.63%).

20 ¹H-NMR (CDCl₃, 400 MHz): 1.52 - 1.80 (m, 6H), 2.61 - 2.71 (m, 2H), 3.68 (s, 2H), 3.76 - 3.84 (m, 1H), 5.06 - 5.19 (m, 1H), 6.63 - 6.72 (m, 3H), 7.24 (s, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.52 - 7.53 (d, J = 6.0 Hz, 1H), 8.47 (d, J = 6.0 Hz, 1H)

25 Mass spectrum (ESI-MS, m/z): 372 (M⁺+1), 370 (M⁺-1)

Example 277: N-(1H-5-Indazolyl)-N-[1-(2-methylbutyl)-3-piperidyl]amine

- 30 [0794] 3-Hydroxypiperidine (1 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and 1-chloro-3-methylbutane (1.07 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.
- 35 [0795] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (7.55 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.
- 40 [0796] This intermediate (723 mg) and 5-aminoindazole (450 mg) were dissolved in titanium tetraisopropoxide (3.6 g), and the mixture was stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (80 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (162 mg, yield 5.66%).

45 ¹H-NMR (CDCl₃, 400 MHz): 0.86 - 0.92 (m, 6H), 1.04 - 1.17 (m, 1H), 1.37 - 1.65 (m, 7H), 2.01 - 2.71 (m, 1H), 2.12 - 2.19 (m, 1H), 2.30 - 2.40 (m, 2H), 2.50 - 2.66 (m, 1H), 3.55 - 3.64 (m, 1H), 6.83 (s, 1H), 6.84 (d, J = 5.1 Hz, 1H), 7.30 (d, J = 9.3 Hz, 1H), 7.87 (s, 1H)

50 Mass spectrum (ESI-MS, m/z): 287 (M⁺+1), 285 (M⁺-1)

Example 278: N-(5-Isoquinolyl)-N-[1-(2-methylbutyl)-3-piperidyl]amine

- 50 [0797] 3-Hydroxypiperidine (1 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and 1-chloro-3-methylbutane (1.07 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.
- 55 [0798] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (7.55 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.

[0799] This intermediate (723 mg) and 5-aminoisoquinoline (487 mg) were dissolved in titanium tetraisopropoxide (3.6 g), and the mixture was stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (80 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (138 mg, yield 4.64%).

⁵ ¹⁰ ¹⁵ ²⁰ ²⁵ ³⁰ ³⁵ ⁴⁰ ⁴⁵ ⁵⁰ ⁵⁵ ⁶⁰ ⁶⁵ ⁷⁰ ⁷⁵ ⁸⁰ ⁸⁵ ⁹⁰ ⁹⁵ ¹⁰⁰ ¹⁰⁵ ¹¹⁰ ¹¹⁵ ¹²⁰ ¹²⁵ ¹³⁰ ¹³⁵ ¹⁴⁰ ¹⁴⁵ ¹⁵⁰ ¹⁵⁵ ¹⁶⁰ ¹⁶⁵ ¹⁷⁰ ¹⁷⁵ ¹⁸⁰ ¹⁸⁵ ¹⁹⁰ ¹⁹⁵ ²⁰⁰ ²⁰⁵ ²¹⁰ ²¹⁵ ²²⁰ ²²⁵ ²³⁰ ²³⁵ ²⁴⁰ ²⁴⁵ ²⁵⁰ ²⁵⁵ ²⁶⁰ ²⁶⁵ ²⁷⁰ ²⁷⁵ ²⁸⁰ ²⁸⁵ ²⁹⁰ ²⁹⁵ ³⁰⁰ ³⁰⁵ ³¹⁰ ³¹⁵ ³²⁰ ³²⁵ ³³⁰ ³³⁵ ³⁴⁰ ³⁴⁵ ³⁵⁰ ³⁵⁵ ³⁶⁰ ³⁶⁵ ³⁷⁰ ³⁷⁵ ³⁸⁰ ³⁸⁵ ³⁹⁰ ³⁹⁵ ⁴⁰⁰ ⁴⁰⁵ ⁴¹⁰ ⁴¹⁵ ⁴²⁰ ⁴²⁵ ⁴³⁰ ⁴³⁵ ⁴⁴⁰ ⁴⁴⁵ ⁴⁵⁰ ⁴⁵⁵ ⁴⁶⁰ ⁴⁶⁵ ⁴⁷⁰ ⁴⁷⁵ ⁴⁸⁰ ⁴⁸⁵ ⁴⁹⁰ ⁴⁹⁵ ⁵⁰⁰ ⁵⁰⁵ ⁵¹⁰ ⁵¹⁵ ⁵²⁰ ⁵²⁵ ⁵³⁰ ⁵³⁵ ⁵⁴⁰ ⁵⁴⁵ ⁵⁵⁰ ⁵⁵⁵ ⁵⁶⁰ ⁵⁶⁵ ⁵⁷⁰ ⁵⁷⁵ ⁵⁸⁰ ⁵⁸⁵ ⁵⁹⁰ ⁵⁹⁵ ⁶⁰⁰ ⁶⁰⁵ ⁶¹⁰ ⁶¹⁵ ⁶²⁰ ⁶²⁵ ⁶³⁰ ⁶³⁵ ⁶⁴⁰ ⁶⁴⁵ ⁶⁵⁰ ⁶⁵⁵ ⁶⁶⁰ ⁶⁶⁵ ⁶⁷⁰ ⁶⁷⁵ ⁶⁸⁰ ⁶⁸⁵ ⁶⁹⁰ ⁶⁹⁵ ⁷⁰⁰ ⁷⁰⁵ ⁷¹⁰ ⁷¹⁵ ⁷²⁰ ⁷²⁵ ⁷³⁰ ⁷³⁵ ⁷⁴⁰ ⁷⁴⁵ ⁷⁵⁰ ⁷⁵⁵ ⁷⁶⁰ ⁷⁶⁵ ⁷⁷⁰ ⁷⁷⁵ ⁷⁸⁰ ⁷⁸⁵ ⁷⁹⁰ ⁷⁹⁵ ⁸⁰⁰ ⁸⁰⁵ ⁸¹⁰ ⁸¹⁵ ⁸²⁰ ⁸²⁵ ⁸³⁰ ⁸³⁵ ⁸⁴⁰ ⁸⁴⁵ ⁸⁵⁰ ⁸⁵⁵ ⁸⁶⁰ ⁸⁶⁵ ⁸⁷⁰ ⁸⁷⁵ ⁸⁸⁰ ⁸⁸⁵ ⁸⁹⁰ ⁸⁹⁵ ⁹⁰⁰ ⁹⁰⁵ ⁹¹⁰ ⁹¹⁵ ⁹²⁰ ⁹²⁵ ⁹³⁰ ⁹³⁵ ⁹⁴⁰ ⁹⁴⁵ ⁹⁵⁰ ⁹⁵⁵ ⁹⁶⁰ ⁹⁶⁵ ⁹⁷⁰ ⁹⁷⁵ ⁹⁸⁰ ⁹⁸⁵ ⁹⁹⁰ ⁹⁹⁵ ¹⁰⁰⁰ ¹⁰⁰⁵ ¹⁰¹⁰ ¹⁰¹⁵ ¹⁰²⁰ ¹⁰²⁵ ¹⁰³⁰ ¹⁰³⁵ ¹⁰⁴⁰ ¹⁰⁴⁵ ¹⁰⁵⁰ ¹⁰⁵⁵ ¹⁰⁶⁰ ¹⁰⁶⁵ ¹⁰⁷⁰ ¹⁰⁷⁵ ¹⁰⁸⁰ ¹⁰⁸⁵ ¹⁰⁹⁰ ¹⁰⁹⁵ ¹¹⁰⁰ ¹¹⁰⁵ ¹¹¹⁰ ¹¹¹⁵ ¹¹²⁰ ¹¹²⁵ ¹¹³⁰ ¹¹³⁵ ¹¹⁴⁰ ¹¹⁴⁵ ¹¹⁵⁰ ¹¹⁵⁵ ¹¹⁶⁰ ¹¹⁶⁵ ¹¹⁷⁰ ¹¹⁷⁵ ¹¹⁸⁰ ¹¹⁸⁵ ¹¹⁹⁰ ¹¹⁹⁵ ¹²⁰⁰ ¹²⁰⁵ ¹²¹⁰ ¹²¹⁵ ¹²²⁰ ¹²²⁵ ¹²³⁰ ¹²³⁵ ¹²⁴⁰ ¹²⁴⁵ ¹²⁵⁰ ¹²⁵⁵ ¹²⁶⁰ ¹²⁶⁵ ¹²⁷⁰ ¹²⁷⁵ ¹²⁸⁰ ¹²⁸⁵ ¹²⁹⁰ ¹²⁹⁵ ¹³⁰⁰ ¹³⁰⁵ ¹³¹⁰ ¹³¹⁵ ¹³²⁰ ¹³²⁵ ¹³³⁰ ¹³³⁵ ¹³⁴⁰ ¹³⁴⁵ ¹³⁵⁰ ¹³⁵⁵ ¹³⁶⁰ ¹³⁶⁵ ¹³⁷⁰ ¹³⁷⁵ ¹³⁸⁰ ¹³⁸⁵ ¹³⁹⁰ ¹³⁹⁵ ¹⁴⁰⁰ ¹⁴⁰⁵ ¹⁴¹⁰ ¹⁴¹⁵ ¹⁴²⁰ ¹⁴²⁵ ¹⁴³⁰ ¹⁴³⁵ ¹⁴⁴⁰ ¹⁴⁴⁵ ¹⁴⁵⁰ ¹⁴⁵⁵ ¹⁴⁶⁰ ¹⁴⁶⁵ ¹⁴⁷⁰ ¹⁴⁷⁵ ¹⁴⁸⁰ ¹⁴⁸⁵ ¹⁴⁹⁰ ¹⁴⁹⁵ ¹⁵⁰⁰ ¹⁵⁰⁵ ¹⁵¹⁰ ¹⁵¹⁵ ¹⁵²⁰ ¹⁵²⁵ ¹⁵³⁰ ¹⁵³⁵ ¹⁵⁴⁰ ¹⁵⁴⁵ ¹⁵⁵⁰ ¹⁵⁵⁵ ¹⁵⁶⁰ ¹⁵⁶⁵ ¹⁵⁷⁰ ¹⁵⁷⁵ ¹⁵⁸⁰ ¹⁵⁸⁵ ¹⁵⁹⁰ ¹⁵⁹⁵ ¹⁶⁰⁰ ¹⁶⁰⁵ ¹⁶¹⁰ ¹⁶¹⁵ ¹⁶²⁰ ¹⁶²⁵ ¹⁶³⁰ ¹⁶³⁵ ¹⁶⁴⁰ ¹⁶⁴⁵ ¹⁶⁵⁰ ¹⁶⁵⁵ ¹⁶⁶⁰ ¹⁶⁶⁵ ¹⁶⁷⁰ ¹⁶⁷⁵ ¹⁶⁸⁰ ¹⁶⁸⁵ ¹⁶⁹⁰ ¹⁶⁹⁵ ¹⁷⁰⁰ ¹⁷⁰⁵ ¹⁷¹⁰ ¹⁷¹⁵ ¹⁷²⁰ ¹⁷²⁵ ¹⁷³⁰ ¹⁷³⁵ ¹⁷⁴⁰ ¹⁷⁴⁵ ¹⁷⁵⁰ ¹⁷⁵⁵ ¹⁷⁶⁰ ¹⁷⁶⁵ ¹⁷⁷⁰ ¹⁷⁷⁵ ¹⁷⁸⁰ ¹⁷⁸⁵ ¹⁷⁹⁰ ¹⁷⁹⁵ ¹⁸⁰⁰ ¹⁸⁰⁵ ¹⁸¹⁰ ¹⁸¹⁵ ¹⁸²⁰ ¹⁸²⁵ ¹⁸³⁰ ¹⁸³⁵ ¹⁸⁴⁰ ¹⁸⁴⁵ ¹⁸⁵⁰ ¹⁸⁵⁵ ¹⁸⁶⁰ ¹⁸⁶⁵ ¹⁸⁷⁰ ¹⁸⁷⁵ ¹⁸⁸⁰ ¹⁸⁸⁵ ¹⁸⁹⁰ ¹⁸⁹⁵ ¹⁹⁰⁰ ¹⁹⁰⁵ ¹⁹¹⁰ ¹⁹¹⁵ ¹⁹²⁰ ¹⁹²⁵ ¹⁹³⁰ ¹⁹³⁵ ¹⁹⁴⁰ ¹⁹⁴⁵ ¹⁹⁵⁰ ¹⁹⁵⁵ ¹⁹⁶⁰ ¹⁹⁶⁵ ¹⁹⁷⁰ ¹⁹⁷⁵ ¹⁹⁸⁰ ¹⁹⁸⁵ ¹⁹⁹⁰ ¹⁹⁹⁵ ²⁰⁰⁰ ²⁰⁰⁵ ²⁰¹⁰ ²⁰¹⁵ ²⁰²⁰ ²⁰²⁵ ²⁰³⁰ ²⁰³⁵ ²⁰⁴⁰ ²⁰⁴⁵ ²⁰⁵⁰ ²⁰⁵⁵ ²⁰⁶⁰ ²⁰⁶⁵ ²⁰⁷⁰ ²⁰⁷⁵ ²⁰⁸⁰ ²⁰⁸⁵ ²⁰⁹⁰ ²⁰⁹⁵ ²¹⁰⁰ ²¹⁰⁵ ²¹¹⁰ ²¹¹⁵ ²¹²⁰ ²¹²⁵ ²¹³⁰ ²¹³⁵ ²¹⁴⁰ ²¹⁴⁵ ²¹⁵⁰ ²¹⁵⁵ ²¹⁶⁰ ²¹⁶⁵ ²¹⁷⁰ ²¹⁷⁵ ²¹⁸⁰ ²¹⁸⁵ ²¹⁹⁰ ²¹⁹⁵ ²²⁰⁰ ²²⁰⁵ ²²¹⁰ ²²¹⁵ ²²²⁰ ²²²⁵ ²²³⁰ ²²³⁵ ²²⁴⁰ ²²⁴⁵ ²²⁵⁰ ²²⁵⁵ ²²⁶⁰ ²²⁶⁵ ²²⁷⁰ ²²⁷⁵ ²²⁸⁰ ²²⁸⁵ ²²⁹⁰ ²²⁹⁵ ²³⁰⁰ ²³⁰⁵ ²³¹⁰ ²³¹⁵ ²³²⁰ ²³²⁵ ²³³⁰ ²³³⁵ ²³⁴⁰ ²³⁴⁵ ²³⁵⁰ ²³⁵⁵ ²³⁶⁰ ²³⁶⁵ ²³⁷⁰ ²³⁷⁵ ²³⁸⁰ ²³⁸⁵ ²³⁹⁰ ²³⁹⁵ ²⁴⁰⁰ ²⁴⁰⁵ ²⁴¹⁰ ²⁴¹⁵ ²⁴²⁰ ²⁴²⁵ ²⁴³⁰ ²⁴³⁵ ²⁴⁴⁰ ²⁴⁴⁵ ²⁴⁵⁰ ²⁴⁵⁵ ²⁴⁶⁰ ²⁴⁶⁵ ²⁴⁷⁰ ²⁴⁷⁵ ²⁴⁸⁰ ²⁴⁸⁵ ²⁴⁹⁰ ²⁴⁹⁵ ²⁵⁰⁰ ²⁵⁰⁵ ²⁵¹⁰ ²⁵¹⁵ ²⁵²⁰ ²⁵²⁵ ²⁵³⁰ ²⁵³⁵ ²⁵⁴⁰ ²⁵⁴⁵ ²⁵⁵⁰ ²⁵⁵⁵ ²⁵⁶⁰ ²⁵⁶⁵ ²⁵⁷⁰ ²⁵⁷⁵ ²⁵⁸⁰ ²⁵⁸⁵ ²⁵⁹⁰ ²⁵⁹⁵ ²⁶⁰⁰ ²⁶⁰⁵ ²⁶¹⁰ ²⁶¹⁵ ²⁶²⁰ ²⁶²⁵ ²⁶³⁰ ²⁶³⁵ ²⁶⁴⁰ ²⁶⁴⁵ ²⁶⁵⁰ ²⁶⁵⁵ ²⁶⁶⁰ ²⁶⁶⁵ ²⁶⁷⁰ ²⁶⁷⁵ ²⁶⁸⁰ ²⁶⁸⁵ ²⁶⁹⁰ ²⁶⁹⁵ ²⁷⁰⁰ ²⁷⁰⁵ ²⁷¹⁰ ²⁷¹⁵ ²⁷²⁰ ²⁷²⁵ ²⁷³⁰ ²⁷³⁵ ²⁷⁴⁰ ²⁷⁴⁵ ²⁷⁵⁰ ²⁷⁵⁵ ²⁷⁶⁰ ²⁷⁶⁵ ²⁷⁷⁰ ²⁷⁷⁵ ²⁷⁸⁰ ²⁷⁸⁵ ²⁷⁹⁰ ²⁷⁹⁵ ²⁸⁰⁰ ²⁸⁰⁵ ²⁸¹⁰ ²⁸¹⁵ ²⁸²⁰ ²⁸²⁵ ²⁸³⁰ ²⁸³⁵ ²⁸⁴⁰ ²⁸⁴⁵ ²⁸⁵⁰ ²⁸⁵⁵ ²⁸⁶⁰ ²⁸⁶⁵ ²⁸⁷⁰ ²⁸⁷⁵ ²⁸⁸⁰ ²⁸⁸⁵ ²⁸⁹⁰ ²⁸⁹⁵ ²⁹⁰⁰ ²⁹⁰⁵ ²⁹¹⁰ ²⁹¹⁵ ²⁹²⁰ ²⁹²⁵ ²⁹³⁰ ²⁹³⁵ ²⁹⁴⁰ ²⁹⁴⁵ ²⁹⁵⁰ ²⁹⁵⁵ ²⁹⁶⁰ ²⁹⁶⁵ ²⁹⁷⁰ ²⁹⁷⁵ ²⁹⁸⁰ ²⁹⁸⁵ ²⁹⁹⁰ ²⁹⁹⁵ ³⁰⁰⁰ ³⁰⁰⁵ ³⁰¹⁰ ³⁰¹⁵ ³⁰²⁰ ³⁰²⁵ ³⁰³⁰ ³⁰³⁵ ³⁰⁴⁰ ³⁰⁴⁵ ³⁰⁵⁰ ³⁰⁵⁵ ³⁰⁶⁰ ³⁰⁶⁵ ³⁰⁷⁰ ³⁰⁷⁵ ³⁰⁸⁰ ³⁰⁸⁵ ³⁰⁹⁰ ³⁰⁹⁵ ³¹⁰⁰ ³¹⁰⁵ ³¹¹⁰ ³¹¹⁵ ³¹²⁰ ³¹²⁵ ³¹³⁰ ³¹³⁵ ³¹⁴⁰ ³¹⁴⁵ ³¹⁵⁰ ³¹⁵⁵ ³¹⁶⁰ ³¹⁶⁵ ³¹⁷⁰ ³¹⁷⁵ ³¹⁸⁰ ³¹⁸⁵ ³¹⁹⁰ ³¹⁹⁵ ³²⁰⁰ ³²⁰⁵ ³²¹⁰ ³²¹⁵ ³²²⁰ ³²²⁵ ³²³⁰ ³²³⁵ ³²⁴⁰ ³²⁴⁵ ³²⁵⁰ ³²⁵⁵ ³²⁶⁰ ³²⁶⁵ ³²⁷⁰ ³²⁷⁵ ³²⁸⁰ ³²⁸⁵ ³²⁹⁰ ³²⁹⁵ ³³⁰⁰ ³³⁰⁵ ³³¹⁰ ³³¹⁵ ³³²⁰ ³³²⁵ ³³³⁰ ³³³⁵ ³³⁴⁰ ³³⁴⁵ ³³⁵⁰ ³³⁵⁵ ³³⁶⁰ ³³⁶⁵ ³³⁷⁰ ³³⁷⁵ ³³⁸⁰ ³³⁸⁵ ³³⁹⁰ ³³⁹⁵ ³⁴⁰⁰ ³⁴⁰⁵ ³⁴¹⁰ ³⁴¹⁵ ³⁴²⁰ ³⁴²⁵ ³⁴³⁰ ³⁴³⁵ ³⁴⁴⁰ ³⁴⁴⁵ ³⁴⁵⁰ ³⁴⁵⁵ ³⁴⁶⁰ ³⁴⁶⁵ ³⁴⁷⁰ ³⁴⁷⁵ ³⁴⁸⁰ ³⁴⁸⁵ ³⁴⁹⁰ ³⁴⁹⁵ ³⁵⁰⁰ ³⁵⁰⁵ ³⁵¹⁰ ³⁵¹⁵ ³⁵²⁰ ³⁵²⁵ ³⁵³⁰ ³⁵³⁵ ³⁵⁴⁰ ³⁵⁴⁵ ³⁵⁵⁰ ³⁵⁵⁵ ³⁵⁶⁰ ³⁵⁶⁵ ³⁵⁷⁰ ³⁵⁷⁵ ³⁵⁸⁰ ³⁵⁸⁵ ³⁵⁹⁰ ³⁵⁹⁵ ³⁶⁰⁰ ³⁶⁰⁵ ³⁶¹⁰ ³⁶¹⁵ ³⁶²⁰ ³⁶²⁵ ³⁶³⁰ ³⁶³⁵ ³⁶⁴⁰ ³⁶⁴⁵ ³⁶⁵⁰ ³⁶⁵⁵ ³⁶⁶⁰ ³⁶⁶⁵ ³⁶⁷⁰ ³⁶⁷⁵ ³⁶⁸⁰ ³⁶⁸⁵ ³⁶⁹⁰ ³⁶⁹⁵ ³⁷⁰⁰ ³⁷⁰⁵ ³⁷¹⁰ ³⁷¹⁵ ³⁷²⁰ ³⁷²⁵ ³⁷³⁰ ³⁷³⁵ ³⁷⁴⁰ ³⁷⁴⁵ ³⁷⁵⁰ ³⁷⁵⁵ ³⁷⁶⁰ ³⁷⁶⁵ ³⁷⁷⁰ ³⁷⁷⁵ ³⁷⁸⁰ ³⁷⁸⁵ ³⁷⁹⁰ ³⁷⁹⁵ ³⁸⁰⁰ ³⁸⁰⁵ ³⁸¹⁰ ³⁸¹⁵ ³⁸²⁰ ³⁸²⁵ ³⁸³⁰ ³⁸³⁵ ³⁸⁴⁰ ³⁸⁴⁵ ³⁸⁵⁰ ³⁸⁵⁵ ³⁸⁶⁰ ³⁸⁶⁵ ³⁸⁷⁰ ³⁸⁷⁵ ³⁸⁸⁰ ³⁸⁸⁵ ³⁸⁹⁰ ³⁸⁹⁵ ³⁹⁰⁰ ³⁹⁰⁵ ³⁹¹⁰ ³⁹¹⁵ ³⁹²⁰ ³⁹²⁵ ³⁹³⁰ ³⁹³⁵ ³⁹⁴⁰ ³⁹⁴⁵ ³⁹⁵⁰ ³⁹⁵⁵ ³⁹⁶⁰ ³⁹⁶⁵ ³⁹⁷⁰ ³⁹⁷⁵ ³⁹⁸⁰ ³⁹⁸⁵ ³⁹⁹⁰ ³⁹⁹⁵ ⁴⁰⁰⁰ ⁴⁰⁰⁵ ⁴⁰¹⁰ ⁴⁰¹⁵ ⁴⁰²⁰ ⁴⁰²⁵ ⁴⁰³⁰ ⁴⁰³⁵ ⁴⁰⁴⁰ ⁴⁰⁴⁵ ⁴⁰⁵⁰ ⁴⁰⁵⁵ ⁴⁰⁶⁰ ⁴⁰⁶⁵ ⁴⁰⁷⁰ ⁴⁰⁷⁵ ⁴⁰⁸⁰ ⁴⁰⁸⁵ ⁴⁰⁹⁰ ⁴⁰⁹⁵ ⁴¹⁰⁰ ⁴¹⁰⁵ ⁴¹¹⁰ ⁴¹¹⁵ ⁴¹²⁰ ⁴¹²⁵ ⁴¹³⁰ ⁴¹³⁵ ⁴¹⁴⁰ ⁴¹⁴⁵ ⁴¹⁵⁰ ⁴¹⁵⁵ ⁴¹⁶⁰ ⁴¹⁶⁵ ⁴¹⁷⁰ ⁴¹⁷⁵ ⁴¹⁸⁰ ⁴¹⁸⁵ ⁴¹⁹⁰ ⁴¹⁹⁵ ⁴²⁰⁰ ⁴²⁰⁵ ⁴²¹⁰ ⁴²¹⁵ ⁴²²⁰ ⁴²²⁵ ⁴²³⁰ ⁴²³⁵ ⁴²⁴⁰ ⁴²⁴⁵ ⁴²⁵⁰ ⁴²⁵⁵ ⁴²⁶⁰ ⁴²⁶⁵ ⁴²⁷⁰ ⁴²⁷⁵ ⁴²⁸⁰ ⁴²⁸⁵ ⁴²⁹⁰ ⁴²⁹⁵ ⁴³⁰⁰ ⁴³⁰⁵ ⁴³¹⁰ ⁴³¹⁵ ⁴³²⁰ ⁴³²⁵ ⁴³³⁰ ⁴³³⁵ ⁴³⁴⁰ ⁴³⁴⁵ ⁴³⁵⁰ ⁴³⁵⁵ ⁴³⁶⁰ ⁴³⁶⁵ ⁴³⁷⁰ ⁴³⁷⁵ ⁴³⁸⁰ ⁴³⁸⁵ ⁴³⁹⁰ ⁴³⁹⁵ ⁴⁴⁰⁰ ⁴⁴⁰⁵ ⁴⁴¹⁰ ⁴⁴¹⁵ ⁴⁴²⁰ ⁴⁴²⁵ ⁴⁴³⁰ ⁴⁴³⁵ ⁴⁴⁴⁰ ⁴⁴⁴⁵ ⁴⁴⁵⁰ ⁴⁴⁵⁵ ⁴⁴⁶⁰ ⁴⁴⁶⁵ ⁴⁴⁷⁰ ⁴⁴⁷⁵ ⁴⁴⁸⁰ ⁴⁴⁸⁵ ⁴⁴⁹⁰ ⁴⁴⁹⁵ ⁴⁵⁰⁰ ⁴⁵⁰⁵ ⁴⁵¹⁰ ⁴⁵¹⁵ ⁴⁵²⁰ ⁴⁵²⁵ ⁴⁵³⁰ ⁴⁵³⁵ ⁴⁵⁴⁰ ⁴⁵⁴⁵ ⁴⁵⁵⁰ ⁴⁵⁵⁵ ⁴⁵⁶⁰ ⁴⁵⁶⁵ ⁴⁵⁷⁰ ⁴⁵⁷⁵ ⁴⁵⁸⁰ ⁴⁵⁸⁵ ⁴⁵⁹⁰ ⁴⁵⁹⁵ ⁴⁶⁰⁰ ⁴⁶⁰⁵ ⁴⁶¹⁰ ⁴⁶¹⁵ ⁴⁶²⁰ ⁴⁶²⁵ ⁴⁶³⁰ ⁴⁶³⁵ ⁴⁶⁴⁰ ⁴⁶⁴⁵ ⁴⁶⁵⁰ ⁴⁶⁵⁵ ⁴⁶⁶⁰ ⁴⁶⁶⁵ ⁴⁶⁷⁰ ⁴⁶⁷⁵ ⁴⁶⁸⁰ ⁴⁶⁸⁵ ⁴⁶⁹⁰ ⁴⁶⁹⁵ ⁴⁷⁰⁰ ⁴⁷⁰⁵ ⁴⁷¹⁰ ⁴⁷¹⁵ ⁴⁷²⁰ ⁴⁷²⁵ ⁴⁷³⁰ ⁴⁷³⁵ ⁴⁷⁴⁰ ⁴⁷⁴⁵ ⁴⁷⁵⁰ ⁴⁷⁵⁵ ⁴⁷⁶⁰ ⁴⁷⁶⁵ ⁴⁷⁷⁰ ⁴⁷⁷⁵ ⁴⁷⁸⁰ ⁴⁷⁸⁵ ⁴⁷⁹⁰ ⁴⁷⁹⁵ ⁴⁸⁰⁰ ⁴⁸⁰⁵ ⁴⁸¹⁰ ⁴⁸¹⁵ ⁴⁸²⁰ ⁴⁸²⁵ ⁴⁸³⁰ ⁴⁸³⁵ ⁴⁸⁴⁰ ⁴⁸⁴⁵ ⁴⁸⁵⁰ ⁴⁸⁵⁵ ⁴⁸⁶⁰ ⁴⁸⁶⁵ ⁴⁸⁷⁰ ⁴⁸⁷⁵ ⁴⁸⁸⁰ ⁴⁸⁸⁵ ⁴⁸⁹⁰ ⁴⁸⁹⁵ ⁴⁹⁰⁰ ⁴⁹⁰⁵ ⁴⁹¹⁰ ⁴⁹¹⁵ ⁴⁹²⁰ ⁴⁹²⁵ ⁴⁹³⁰ ⁴⁹³⁵ ⁴⁹⁴⁰ ⁴⁹⁴⁵ ⁴⁹⁵⁰ ⁴⁹⁵⁵ ⁴⁹⁶⁰ ⁴⁹⁶⁵ ⁴⁹⁷⁰ ⁴⁹⁷⁵ ⁴⁹⁸⁰ ⁴⁹⁸⁵ ⁴⁹⁹⁰ ⁴⁹⁹⁵ ⁵⁰⁰⁰ ⁵⁰⁰⁵ ⁵⁰¹⁰ ⁵⁰¹⁵ ⁵⁰²⁰ ⁵⁰²⁵ ⁵⁰³⁰ ⁵⁰³⁵ ⁵⁰⁴⁰ ⁵⁰⁴⁵ ⁵⁰⁵⁰ ⁵⁰⁵⁵ ⁵⁰⁶⁰ ⁵⁰⁶⁵ ⁵⁰⁷⁰ ⁵⁰⁷⁵ ⁵⁰⁸⁰ ⁵⁰⁸⁵ ⁵⁰⁹⁰ ⁵⁰⁹⁵ ⁵¹⁰⁰ ⁵¹⁰⁵ ⁵¹¹⁰ ⁵¹¹⁵ ⁵¹²⁰ ⁵¹²⁵ ⁵¹³⁰ ⁵¹³⁵ ⁵¹⁴⁰ ⁵¹⁴⁵ ⁵¹⁵⁰ ⁵¹⁵⁵ ⁵¹⁶⁰ ⁵¹⁶⁵ ⁵¹⁷⁰ ⁵¹⁷⁵ ⁵¹⁸⁰ ⁵¹⁸⁵ ⁵¹⁹⁰ ⁵¹⁹⁵ ⁵²⁰⁰ ⁵²⁰⁵ ⁵²¹⁰ ⁵²¹⁵ ⁵²²⁰ ⁵²²⁵ ⁵²³⁰ ⁵²³⁵ ⁵²⁴⁰ ⁵²⁴⁵ ⁵²⁵⁰ ⁵²⁵⁵ ⁵²⁶⁰ ⁵²⁶⁵ ⁵²⁷⁰ ⁵²⁷⁵ ⁵²⁸⁰ ⁵²⁸⁵ ⁵²⁹⁰ ⁵²⁹⁵ ⁵³⁰⁰ ⁵³⁰⁵ ⁵³¹⁰ ⁵³¹⁵ ⁵³²⁰ ⁵³²⁵ ⁵³³⁰ ⁵³³⁵ ⁵³⁴⁰ ⁵³⁴⁵ ⁵³⁵⁰ ⁵³⁵⁵ ⁵³⁶⁰ ⁵³⁶⁵ ⁵³⁷⁰ ⁵³⁷⁵ ⁵³⁸⁰ ⁵³⁸⁵ ⁵³⁹⁰ ⁵³⁹⁵ ⁵⁴⁰⁰ ⁵⁴⁰⁵ ⁵⁴¹⁰ ⁵⁴¹⁵ ⁵⁴²⁰ ⁵⁴²⁵ ⁵⁴³⁰ ⁵⁴³⁵ ⁵⁴⁴⁰ ⁵⁴⁴⁵ ⁵⁴⁵⁰ ⁵⁴⁵⁵ ⁵⁴⁶⁰ ⁵⁴⁶⁵ ⁵⁴⁷⁰ ⁵⁴⁷⁵ ⁵⁴⁸⁰ ⁵⁴⁸⁵ ⁵⁴⁹⁰ ⁵⁴⁹⁵ ⁵⁵⁰⁰ ⁵⁵⁰⁵ ⁵⁵¹⁰ ⁵⁵¹⁵ ⁵⁵²⁰ ⁵⁵²⁵ ⁵⁵³⁰ ⁵⁵³⁵ ⁵⁵⁴⁰ ⁵⁵⁴⁵ ⁵⁵⁵⁰ ⁵⁵⁵⁵ ⁵⁵⁶⁰ ⁵⁵⁶⁵ ⁵⁵⁷⁰ ⁵⁵⁷⁵ ⁵⁵⁸⁰ ⁵⁵⁸⁵ ⁵⁵⁹⁰ ⁵⁵⁹⁵ ⁵⁶⁰⁰ ⁵⁶⁰⁵ ⁵⁶¹⁰ ⁵⁶¹⁵ ⁵⁶²⁰ ⁵⁶²⁵ ⁵⁶³⁰ ⁵⁶³⁵ ⁵⁶⁴⁰ ⁵⁶⁴⁵ ⁵⁶⁵⁰ ⁵⁶⁵⁵ ⁵⁶⁶⁰ ⁵⁶⁶⁵ <sup

and the mixture was stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (128 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (376 mg, yield 12.5%)

⁵ ¹H-NMR (CDCl₃, 400 MHz): 0.03 - 0.93 (m, 6H), 1.04 - 1.08 (m, 1H), 1.19 - 1.42 (m, 4H), 2.01 - 2.17 (m, 2H), 2.37 - 2.60 (m, 3H), 3.56 - 3.63 (m, 1H), 6.82 - 6.84 (m, 2H), 7.29 (d, J = 9.5, 1H), 7.87 (s, 1H)
Mass spectrum (ESI-MS, m/z): 301 (M⁺+1)

¹⁰ Example 282: N-(1H-5-Indazolyl)-N-[1-(2,4,6-trifluorobenzyl)-3-piperidyl]amine

[0807] 3-Hydroxypiperidine (130 mg) and potassium carbonate (659 mg) were dissolved in acetonitrile (5 ml), and 2,4,6-trifluorobenzyl bromide (290 mg) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.

[0808] ¹⁵ This intermediate and triethylamine (275 mg) were dissolved in anhydrous dimethyl sulfoxide (1.73 ml), and a sulfur trioxide-trimethylamine complex (379 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was then concentrated to give an intermediate.

[0809] ²⁰ This intermediate (290 mg) was dissolved in titanium tetraisopropoxide (1.45 g). 5-Aminoindazole (121 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (21 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was then diluted with ethyl acetate, and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (58 mg, yield 12.5%).

²⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.57 - 1.74 (m, 5H), 2.45 (m, 3H), 2.74 - 2.77 (m, 1H), 3.59 - 3.65 (m, 3H), 6.61 - 6.69 (m, 2H), 6.80 - 6.83 (m, 2H), 7.27 - 7.30 (m, 1H), 7.86 (s, 1H)

Mass spectrum (ESI-MS, m/z): 361 (M⁺+1)

³⁰ Example 283: N-(1H-5-Indazolyl)-N-[1-(2,4,6-trifluorobenzyl)-4-piperidyl]amine

[0810] 4-Piperidone hydrochloride monohydrate (198 mg) and potassium carbonate (659 mg) were dissolved in acetonitrile (5 ml), and 2,4,6-trifluorobenzyl bromide (290 mg) was added dropwise to the solution at room temperature.

³⁵ The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.

[0811] ⁴⁰ This intermediate and triethylamine (275 mg) were dissolved in anhydrous dimethyl sulfoxide (1.73 ml), and a sulfur trioxide-trimethylamine complex (379 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.

[0812] ⁴⁵ This intermediate (292 mg) was dissolved in titanium tetraisopropoxide (1.45 g). 5-Aminoindazole (128 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (23 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate, and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (215 mg, yield 46.2%).

⁵⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.43 - 1.62 (m, 2H), 2.07 - 2.11 (m, 2H), 2.24 - 2.30 (m, 2H), 2.91 - 2.94 (m, 2H), 3.21 - 3.29 (m, 1H), 6.65 - 6.72 (m, 2H), 6.77 - 6.81 (m, 2H), 7.28 - 7.30 (m, 1H), 7.86 (s, 1H)

Mass spectrum (ESI-MS, m/z): 361 (M⁺+1)

Example 284: N-(1H-5-Indazolyl)-N-(1-methyl-4-piperidyl)amine

[0813] ⁵⁵ 1-Methyl-4-piperidone (300 mg) was dissolved in titanium tetraisopropoxide (1.5 g). 5-Aminoindazole (282 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (50 mg) were added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate, and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by

column chromatography on silica gel [chloroform/methanol] to give the title compound (202 mg, yield 41.4%).

¹H-NMR (CDCl₃, 400 MHz): 1.47 - 1.57 (m, 2H), 2.10 - 2.18 (m, 4H), 2.30 (s, 3H), 2.83 - 2.86 (m, 2H), 3.28 - 3.33 (m, 1H), 6.80 - 6.82 (m, 2H), 7.28 - 7.31 (m, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 230 (M⁺+1)

5

Example 285: N-(1H-5-Indazolyl)-N-(1-propyl-3-piperidyl)amine

[0814] 3-Hydroxypiperidine (1.00 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and 3-bromopropane (1.23 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.

[0815] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen carbonate solution was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.

[0816] This intermediate and 5-aminoindazole (200 mg) were dissolved in titanium tetraisopropoxide (1.0 g), and the mixture was stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (100 mg) were added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (100 mg, yield 3.87%).

¹H-NMR (CDCl₃, 400 MHz): 0.90 (t, J = 7.6 Hz, 3H), 1.51 - 2.07 (m, 4H), 2.07 - 2.21 (m, 4H), 2.36 - 2.40 (m, 2H), 2.96 - 2.99 (m, 2H), 3.29 - 3.36 (m, 1H), 6.75 - 6.81 (m, 2H), 7.25 (d, J = 12.0 Hz, 1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 259 (M⁺+1)

25

Example 286: N-(1H-5-Indazolyl)-N-(1-propyl-4-piperidyl)amine

[0817] 4-Piperidone hydrochloride monohydrate (1.53 g) and potassium carbonate (2.76 g) were dissolved in anhydrous N,N-dimethylformamide, and 1-bromopropane (1.29 g) was added dropwise to the solution at room temperature. The reaction solution was stirred at room temperature for 18 hr. Ethyl acetate was then added to the solution, and the mixture was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The organic layer was concentrated under the reduced pressure to give an intermediate.

[0818] This intermediate (1.03 g) was dissolved in titanium tetraisopropoxide (5.5 g). 5-Aminoindazole (971 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (276 mg) were then added solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (1.3 g, yield 50.3%).

¹H-NMR (CDCl₃, 400 MHz): 0.91 (t, J = 7.3 Hz, 3H), 1.48 - 1.59 (m, 4H), 2.10 - 2.18 (m, 4H), 2.33 - 2.37 (m, 2H), 2.92 - 2.95 (m, 2H), 3.30 - 3.36 (m, 1H), 6.78 - 6.82 (m, 2H), 7.27 - 7.29 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 1.0 Hz, 1H)

Mass spectrum (ESI-MS, m/z): 259 (M⁺+1)

40

Example 287: N-[1-(Cyclopropylmethyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0819] 4-Piperidone hydrochloride monohydrate (1.14 g) and potassium carbonate (1.38 g) were dissolved in anhydrous acetonitrile, and (bromomethyl)cyclopropane (1 g) was added dropwise to the solution at room temperature. The reaction solution was stirred at room temperature for 18 hr. Ethyl acetate was then added to the solution, and the mixture was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The organic layer was concentrated under the reduced pressure to give an intermediate.

[0820] This intermediate was dissolved in titanium tetraisopropoxide (4.3 g). 5-Aminoindazole (600 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (170 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (338 mg, yield 16.9%).

¹H-NMR (CDCl₃, 400 MHz): 0.11 - 0.13 (m, 2H), 0.49 - 0.57 (m, 2H), 0.86 - 0.93 (m, 1H), 1.50 - 1.59 (m, 2H), 2.11 - 2.22 (m, 4H), 2.29 - 2.31 (m, 2H), 3.04 - 3.07 (m, 2H), 3.29 - 3.35 (m, 1H), 6.79 - 6.82 (m, 2H), 7.28 - 7.31 (m,

45

1H), 7.88 (s, 1H)

Mass spectrum (ESI-MS, m/z): 271 (M⁺⁺1)

Example 288: N-[1-(2-Fluoroethyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0821] 4-Piperidone hydrochloride monohydrate (1.53 g) and potassium carbonate (2.76 g) were dissolved in anhydrous acetonitrile. 1-Bromo-2-fluoroethane (1.27 g) was added dropwise to the solution at room temperature. The reaction solution was stirred at room temperature for 18 hr. Ethyl acetate was then added to the solution, and the mixture was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The organic layer was concentrated under the reduced pressure to give an intermediate.

[0822] This intermediate (257 mg) was dissolved in titanium tetraisopropoxide (1.2 g). 5-Aminoindazole (188 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (33 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (80 mg, yield 3.05%).

¹H-NMR (CDCl₃, 400 MHz): 1.50 - 1.59 (m, 2H), 2.10 - 2.14 (m, 2H), 2.26 - 2.32 (m, 2H), 2.71 (t, J = 4.9 Hz, 1H), 2.79 (t, J = 4.9 Hz, 1H), 2.96 - 2.99 (m, 2H), 3.30 - 3.37 (m, 1H), 4.53 (t, J = 4.9 Hz, 1H), 4.65 (t, J = 4.9 Hz, 1H), 6.79 - 6.82 (m, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.89 (s, 1H)

Mass spectrum (ESI-MS, m/z): 263 (M⁺⁺1)

Example 289: N-[1-(3-Fluoropropyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0823] 4-Piperidone hydrochloride monohydrate (768 mg) and potassium carbonate (1.38 g) were dissolved in anhydrous acetonitrile. 1-Bromo-3-fluoroethane (705 mg) was added dropwise to the solution at room temperature. The reaction solution was stirred at room temperature for 18 hr. Ethyl acetate was then added to the solution, and the mixture was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The organic layer was concentrated under the reduced pressure to give an intermediate.

[0824] This intermediate (510 mg) was dissolved in titanium tetraisopropoxide (2.6 g). 5-Aminoindazole (464 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (66 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (710 mg, yield 51.4%).

¹H-NMR (CDCl₃, 400 MHz): 1.46 - 1.55 (m, 2H), 1.86 - 1.98 (m, 2H), 2.10 - 2.20 (m, 4H), 2.51 (t, J = 7.1 Hz, 2H), 2.90 - 2.92 (m, 2H), 3.29 - 3.36 (m, 1H), 4.46 (t, J = 6.1 Hz, 1H), 4.57 (t, J = 6.1 Hz, 1H), 6.79 - 6.82 (m, 2H), 7.29 (d, J = 8.5 Hz, 1H), 7.89 (m, 1H)

Mass spectrum (ESI-MS, m/z): 277 (M⁺⁺1)

Example 290: N-(1H-5-Indazolyl)-N-[1-(3,3,3-trifluoropropyl)-4-piperidyl]amine

[0825] 4-Piperidone hydrochloride monohydrate (768 mg) and potassium carbonate (1.38 g) were dissolved in anhydrous acetonitrile. 1-Bromo-3,3,3-trifluoropropane (884 mg) was added dropwise to the solution at room temperature. The reaction solution was stirred at room temperature for 18 hr. Ethyl acetate was then added to the solution, and the mixture was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The organic layer was concentrated under the reduced pressure to give an intermediate.

[0826] This intermediate (430 mg) was dissolved in titanium tetraisopropoxide (2.6 g). 5-Aminoindazole (234 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (83.6 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (160 mg, yield 10.2%).

¹H-NMR (CDCl₃, 400 MHz): 1.44 - 1.51 (m, 2H), 2.05 - 2.17 (m, 4H), 2.24 - 2.36 (m, 2H), 2.59 - 2.62 (m, 2H), 2.82 - 2.84 (m, 2H), 3.27 (m, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.92 (s, 1H)

Mass spectrum (ESI-MS, m/z): 313 (M⁺⁺1)

Example 291: N-[1-(4,4-Dimethylpentyl)-4-piperidyl]-N-(1H-5-indazolyl)amine

[0827] 4-Piperidone hydrochloride monohydrate (768 mg) and potassium carbonate (1.38 g) were dissolved in anhydrous acetonitrile, and 1-bromo-4,4,4-trifluorobutane (955 mg) was added dropwise to the solution at room temperature. The reaction solution was stirred at room temperature for 18 hr. Ethyl acetate was then added, and the mixture was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The organic layer was concentrated under the reduced pressure to give an intermediate.

[0828] This intermediate (684 mg) was dissolved in titanium tetraisopropoxide (3.4 g). 5-Aminoindazole (348 mg) was added to the solution, and the mixture was stirred at room temperature for 18 hr. Methanol and sodium borohydride (124 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (522 mg, yield 38.3%).

¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.52 (m, 2H), 1.71 - 1.78 (m, 2H), 2.08 - 2.16 (m, 6H), 2.38 - 2.41 (m, 2H), 2.85 - 2.88 (m, 2H), 3.28 - 3.33 (m, 1H), 6.76 (d, J = 8.8 Hz, 1H), 6.81 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.91 (s, 1H)
Mass spectrum (ESI-MS, m/z): 273 (M⁺+1)

Example 292: N-[1-(3-Fluoropropyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0829] 3-Hydroxypiperidine (718 mg) and potassium carbonate (1.96 g) were dissolved in acetonitrile. 1-Bromo-3-fluoropropane (1.0 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.

[0830] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.

[0831] This intermediate and 5-aminoindazole (150 mg) were dissolved in titanium tetraisopropoxide (750 mg), and the mixture was stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (100 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (62 mg, yield 3.16%).

¹H-NMR (CDCl₃, 400 MHz): 1.59 (m, 2H), 1.75 - 1.77 (m, 2H), 1.83 - 1.96 (m, 2H), 2.37 - 2.54 (m, 4H), 2.75 (m, 2H), 3.61 (m, 1H), 4.46 (t, J = 5.9 Hz, 1H), 4.58 (t, J = 6.1 Hz, 1H), 6.82 - 6.85 (m, 2H), 7.29 - 7.31 (m, 1H), 7.88 (s, 1H)
Mass spectrum (ESI-MS, m/z): 277 (M⁺+1)

Example 293: N-[1-(2-Chloro-4-fluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0832] 3-Hydroxypiperidine (1 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and 2-chloro-4-fluorobenzyl bromide (2.23 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.

[0833] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.

[0834] This intermediate (317 mg) and 5-aminoindazole (139 mg) were dissolved in titanium tetraisopropoxide (1.6 g), and the mixture was stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (100 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (150 mg, yield 4.18%).

¹H-NMR (CDCl₃, 400 MHz): 1.56 - 1.74 (m, 5H), 2.42 - 2.49 (m, 2H), 2.73 - 2.76 (m, 1H), 3.56 (s, 2H), 3.59 - 3.62 (m, 1H), 6.79 - 6.83 (m, 1H), 6.94 (dt, J = 2.7, 8.3 Hz, 1H), 7.12 (dd, J = 2.7, 8.5 Hz, 2H), 7.27 - 7.30 (m, 1H), 7.39 - 7.42 (m, 1H), 7.86 (d, J = 1.0 Hz, 1H)

Mass spectrum (ESI-MS, m/z): 359 (M⁺+1)

Example 294: Methyl 2-(3,4-difluoropentyl)-2-[3-(1H-5-indazolylamino)piperidino]acetate

- 5 [0835] 3,4-Difluorophenylacetic acid (3.42 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and methyl iodide (2.82 g) was added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.
- 10 [0836] This intermediate (2.02 g) was dissolved in carbon tetrachloride. N-Bromosuccinimide (2.88 g) was added to the solution, and the mixture was refluxed for 18 hr. The reaction solution was then filtered through Celite, and the filtrate was concentrated to give an intermediate.
- 15 [0837] This intermediate (1.60 g) and potassium carbonate (1.73 g) were dissolved in acetonitrile (10 ml), and 3-hydroxypiperidine (631 mg) was added to the solution. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.
- 20 [0838] This intermediate (2.02 g) was dissolved in anhydrous dimethyl sulfoxide, and triethylamine (552 mg) and sulfur trioxide-trimethylamine complex (758 mg) were then added to the solution under an argon atmosphere. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.
- 25 [0839] This intermediate (763 mg) and 5-aminoindazole (287 mg) were dissolved in titanium tetraisopropoxide (3.87 g), and the mixture was stirred at room temperature for 18 hr. A minor amount of methanol and sodium borohydride (101 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (345 mg, yield 0.43%).

¹H-NMR (CDCl₃, 400 MHz): 1.59 - 1.63 (m, 2H), 1.76 - 1.78 (m, 2H), 2.31 - 2.49 (m, 4H), 3.69 (d, J = 6.4 Hz, 2H), 6.76 - 6.84 (m, 2H), 7.07 - 7.13 (m, 2H), 7.28 - 7.37 (m, 1H), 7.86 (s, 1H)

Mass spectrum (ESI-MS, m/z): 399 (M⁺+1)

30 Example 295: N-(1H-5-Indazolyl)-N-{1-[(2S)-2-methylbutyl]-3-piperidyl}amine

- 35 [0840] 3-Hydroxypiperidine (1 g) and potassium carbonate (2.76 g) were dissolved in acetonitrile (10 ml), and a solution (15.1 ml) of (S)-(+)-1-bromo-2-methylbutane (1.51 g) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give an intermediate.
- 40 [0841] This intermediate and triethylamine (1.78 g) were dissolved in anhydrous dimethyl sulfoxide (7.55 ml), and a sulfur trioxide-trimethylamine complex (2.45 g) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (7.55 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give an intermediate.
- 45 [0842] This intermediate and 5-aminoindazole (939 mg) were dissolved in titanium tetraisopropoxide (4.7 g), and the mixture was stirred at room temperature for 18 hr. Methanol (0.94 ml) and sodium borohydride (134 mg) were then added to the reaction solution, and the mixture was stirred for 18 hr. The reaction solution was diluted with ethyl acetate (40 ml), and a minor amount of water was added thereto, and the mixture was then filtered under the reduced pressure. The filtrate was concentrated under the reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol] to give the title compound (253 mg, yield 8.8%).

¹H-NMR (CDCl₃, 400 MHz): 0.89 (dd, J = 7.3, 13.9 Hz, 3H), 0.89 (d, J = 5.8 Hz, 3H), 1.06 - 1.15 (m, 1H), 1.37 - 1.79 (m, 6H), 2.01 - 2.08 (m, 2H), 2.12 - 2.19 (m, 2H), 2.52 - 2.69 (m, 1H), 3.56 - 3.62 (m, 1H), 6.83 (s, 1H), 6.84 (dd, J = 2.2, 6.6 Hz, 1H), 7.29 (d, J = 9.5 Hz, 1H), 7.87 (s, 1H)

50 Mass spectrum (ESI-MS, m/z): 278 (M⁺+1)

Example 296: N-(1-Benzyl-3-methyl-4-piperidyl)-N-(1H-5-indazolyl)amine

- 55 [0843] 1-Benzyl-3-methyl-4-piperidone (152.7 mg), 5-aminoindazole (100 mg), and acetic acid (0.02 ml) were dissolved in methanol (10 ml). Acetic acid (five drops) was added to the solution, and a borane-pyridine complex (0.06 ml) was then added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, a saturated aqueous sodium hydrogencarbonate solution (1 ml) was added thereto, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and

saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform/methanol] to give the title compound (95.3 mg, yield 65%).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.45 - 1.60 (m, 2H), 2.07 - 2.15 (m, 2H), 2.18 - 2.32 (m, 2H), 2.82 - 2.92 (m, 2H),

3.30 - 3.40 (m, 1H), 3.63 (s, 2H), 6.79 - 6.84 (m, 2H), 7.31 (d, J = 9.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.1 Hz, 1H), 7.88 (s, 1H), 8.12 (d, J = 6.9 Hz, 1H), 8.23 (s, 1H)

Mass spectrum (ESI-MS, m/z): 320 (M⁺+1)

Example 297: N-[1-(4-Fluorobenzyl)-3-piperidyl]-N-(5-isoquinolyl)amine

¹⁰ [0844] 3-Hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) were dissolved in dimethylformamide (10 ml), and a solution (10 ml) of 4-fluorobenzyl chloride (312.2 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite. The filtrate was concentrated to give intermediate A.

¹⁵ [0845] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was then concentrated to give intermediate B.

²⁰ [0846] Titanium isopropoxide was added to this intermediate B and 5-aminoisoquinoline (210.5 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (166 mg).

²⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.70 - 1.82 (1H, m), 1.85 - 2.00 (1H, m), 2.00 - 2.10 (1H, m), 2.97 (2H, q, J = 11.7 Hz), 3.39 (1H, d, J = 12.2 Hz), 3.65 (1H, d, J = 11.7 Hz), 4.15 - 4.30 (1H, m), 4.25 - 4.42 (2H, m), 7.02 - 7.17 (3H, m), 7.36 (1H, d, J = 8.1 Hz), 7.59 - 7.65 (2H, m), 7.75 (1H, t, J = 8.1 Hz), 8.37 (1H, d, J = 6.8 Hz), 8.66 (1H, d, J = 6.8 Hz), 9.49 (1H, s)

Mass spectrum (ESI-MS, m/z): 335 (M⁺+1)

Example 298: N-(1H-5-Indazolyl)-N-[1-[4-(trifluoromethyl)benzyl]-3-piperidyl]amine

³⁵ [0847] 3-Hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) were dissolved in dimethylformamide (10 ml), and a solution (10 ml) of 4-trifluoromethylbenzyl chloride (421.4 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

⁴⁰ [0848] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

⁴⁵ [0849] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (210.5 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (154 mg).

⁵⁰ ¹H-NMR (CD₃OD, 400 MHz): 1.75 - 2.00 (2H, m), 2.00 - 2.23 (2H, m), 3.00 - 3.20 (1H, m), 3.20 - 3.45 (2H, m), 3.50 - 3.60 (1H, m), 4.09 (1H, s), 4.47 (1H, s), 7.42 (1H, d, J = 8.5 Hz), 7.61 (3H, d, J = 8.1 Hz), 7.66 - 7.75 (1H, m), 7.74 (2H, d, J = 7.1 Hz), 8.19 (1H, s)

Mass spectrum (ESI-MS, m/z): 374 (M⁺+1)

Example 299: N-(5-Isoquinolyl)-N-[1-[4-(trifluoro-methyl)benzyl]-3-piperidyl]amine

⁵⁵ [0850] 3-Hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) were dissolved in dimethylformamide (10

ml), and a solution (10 ml) of 4-trifluoromethylbenzyl chloride (421.4 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0851] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0852] Titanium isopropoxide was added to this intermediate B and 5-aminoisoquinoline (210.5 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (163 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.43 - 1.56 (m, 2H), 1.60 - 1.73 (m, 2H), 2.23 - 2.40 (m, 3H), 2.61 - 2.80 (m, 1H), 3.33 - 3.47 (m, 2H), 3.48 - 3.58 (m, 1H), 3.72 (s, 3H), 6.74 (s, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 385 (M⁺⁺1)

Example 300: N-[1-(3,4-Difluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0853] 3-Hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) were dissolved in dimethylformamide (10 ml), and a solution (1 ml) of 3,4-difluorobenzyl bromide (448.4 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0854] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0855] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (210.5 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (181 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.30 - 1.40 (1H, m), 1.59 - 1.69 (1H, m), 1.74 - 1.80 (1H, m), 1.91 - 1.94 (1H, m), 2.00 (1H, m), 2.18 (1H, t, J = 7.0 Hz), 2.63 (1H, m), 2.93 (1H, d, J = 10.0 Hz), 3.30 - 3.32 (1H, m), 3.48 (1H, q, J = 8.0 Hz), 6.85 (1H, d, J = 1.5 Hz), 6.92 (1H, dd, J = 2.2, 8.8 Hz), 7.07 - 7.10 (1H, m), 7.14 (1H, dd, J = 8.1, 10.2 Hz), 7.26 (1H, ddd, J = 2.0, 8.1, 11.5 Hz), 7.31 (1H, d, J = 8.8 Hz), 7.77 (1H, d, J = 1.0 Hz)

Mass spectrum (ESI-MS, m/z): 342 (M⁺⁺1)

Example 301: M-[1-(3,4-Difluorobenzyl)-3-piperidyl]-N-(5-isoquinolyl)amine

[0856] 3-Hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) were dissolved in dimethylformamide (10 ml), and a solution (10 ml) of 3,4-difluorobenzyl chloride (448.4 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0857] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogencarbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was then concentrated to give intermediate B.

[0858] Titanium isopropoxide was added to this intermediate B and 5-aminoisoquinoline (210.5 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction

mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (156 mg).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.43 - 1.56 (m, 2H), 1.60 - 1.73 (m, 2H), 2.23 - 2.40 (m, 3H), 2.61 - 2.80 (m, 1H), 3.33 - 3.47 (m, 2H), 3.48 - 3.58 (m, 1H), 3.72 (s, 3H), 6.74 (s, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H)

Mass spectrum (ESI-MS, m/z): 353 (M⁺+1)

¹⁰ Example 302: N-[1-[4-Fluoro-3-(trifluoromethyl)benzyl]-3-piperidyl]-N-(1H-5-indazolyl)amine

[0859] 3-Hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) were dissolved in dimethylformamide (10 ml), and a solution (10 ml) of 4-fluoro-3-trifluoromethylbenzyl chloride (556.7 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0860] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0861] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (210.5 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (161 mg).

³⁰ ¹H-NMR (CD₃OD, 400 MHz): 1.80 - 1.90 (1H, m), 1.90 - 2.05 (1H, m), 2.05 - 2.11 (2H, m), 3.00 - 3.10 (1H, m), 3.10 - 3.35 (1H, m), 3.35 - 3.50 (1H, m), 3.60 - 3.70 (1H, m), 4.10 - 4.20 (1H, m), 4.51 (2H, q, J = 13.2 Hz), 7.43 (1H, t, J = 9.3 Hz), 7.49 (1H, d, J = 9.0 Hz), 7.70 (2H, d, J = 9.0 Hz), 7.93 - 7.98 (1H, m), 8.02 (1H, d, J = 6.3 Hz), 8.33 (1H, d, J = 0.7 Hz)

Mass spectrum (ESI-MS, m/z): 392 (M⁺+1)

Example 303: N-[1-(3,4-Dichlorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0862] 3-Hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) were dissolved in dimethylformamide (1 ml), and a solution (1 ml) of 3, 4-dichlorobenzyl chloride (423.4 mg) in acetonitrile was added dropwise thereto at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0863] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0864] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (210.5 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (133 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.70 - 2.20 (4H, m), 3.00 - 3.20 (1H, m), 3.40 - 3.55 (1H, m), 3.40 - 3.55 (1H, m), 3.65 (1H, bs), 4.15 (1H, bs), 4.43 (2H, q, J = 10.5 Hz), 7.51 (1H, d, J = 9.27 Hz), 7.57 (1H, s), 7.71 (1H, d, J = 9.0 Hz), 7.85 (1H, s), 8.33 (1H, d, J = 0.7 Hz)

Mass spectrum (ESI-MS, m/z): 375 (M⁺+1)

Example 304: N-[1-(4-Chlorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0865] 4-Chlorobenzyl chloride (318.3 mg) was added dropwise to a solution (10 ml) of 3-hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0866] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0867] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (171 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.30 - 1.45 (1H, m), 1.59 - 1.70 (1H, m), 1.75 - 1.83 (1H, m), 1.94 - 1.97 (1H, m), 2.00 - 2.10 (1H, m), 2.24 (1H, t, J = 9.3 Hz), 2.71 (1H, d, J = 10.7 Hz), 3.00 (1H, d, J = 9.3 Hz), 3.48 - 3.52 (1H, m), 3.56 (2H, q, J = 9.3 Hz), 6.84 (1H, d, J = 2.0 Hz), 6.91 (1H, dd, J = 2.0, 9.0 Hz), 7.31 (1H, d, J = 1.7 Hz), 7.77 (1H, d, J = 1.0 Hz)

Mass spectrum (ESI-MS, m/z): 340 (M⁺+1)

Example 305: N-(1H-5-Indazolyl)-N-[1-(phenylsulfonyl)-3-piperidyl]amine

[0868] Benzenesulfonyl chloride (382.8 mg) was added dropwise to a solution (20 ml) of 3-hydroxypiperidine (200 mg) and triethylamine (0.33 ml) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give intermediate A.

[0869] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0870] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was then added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (146.7 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.49 - 1.56 (1H, m), 1.69 - 1.75 (1H, m), 1.83 - 1.90 (2H, m), 2.70 (1H, dd, J = 7.3, 11.2 Hz), 2.89 (1H, dd, J = 3.7, 8.3 Hz), 3.23 (1H, dd, J = 6.6, 10.7 Hz), 3.54 (1H, dd, J = 3.7, 11.5 Hz), 3.62 (1H, m), 6.84 (1H, dd, J = 2.2, 8.8 Hz), 6.89 (1H, d, J = 2.2 Hz), 7.35 (1H, d, J = 8.8 Hz), 7.53 (2H, t, J = 7.1 Hz), 7.61 (1H, t, J = 7.3 Hz), 7.76 (2H, d, J = 7.1 Hz), 7.91 (1H, s)

Mass spectrum (ESI-MS, m/z): 358 (M⁺+1)

Example 306: N-(1H-5-Indazolyl)-N-[1-[(4-methylphenyl)sulfonyl]-3-piperidyl]amine

[0871] p-Toluenesulfonyl chloride (423.3 mg) was added dropwise to a solution (20 ml) of 3-hydroxypiperidine (200 mg) and triethylamine (0.33 ml) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give intermediate A.

[0872] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0873] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (212 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.40 - 1.44 (1H, m), 1.60 - 1.70 (2H, m), 2.36 (3H, s), 2.61 (1H, dd, J = 7.1, 11.5 Hz), 2.80 (1H, t, J = 8.5 Hz), 3.12 (1H, dd, J = 7.1, 8.5 Hz), 3.43 (1H, d, J = 11.5 Hz), 3.54 (1H, m), 6.75 (1H, dd, J = 2.0, 8.5 Hz), 6.78 (1H, s), 7.24 (2H, d, J = 8.5 Hz), 7.25 (1H, d, J = 8.3 Hz), 7.56 (2H, d, J = 8.3 Hz), 7.83 (1H, s)

Mass spectrum (ESI-MS, m/z): 370 (M⁺+1)

Example 307: N-[1-[(4-Chlorophenyl)sulfonyl-3-piperidyl]-N-(1H-5-indazolyl)amine

[0874] 4-Fluorobenzenesulfonyl chloride (423.3 mg) was added dropwise to a solution (20 ml) of 3-hydroxypiperidine (200 mg) and triethylamine (0.33 ml) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give intermediate A.

[0875] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0876] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (216.2 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.40 - 1.51 (1H, m), 1.62 - 1.75 (1H, m), 1.89 - 1.90 (2H, m), 1.90 - 2.05 (1H, m), 2.64 (1H, t, J = 11.0 Hz), 2.84 (1H, t, J = 8.5 Hz), 3.18 - 3.25 (1H, m), 3.52 (1H, d, J = 11.0 Hz), 6.79 (1H, d, J = 8.8 Hz), 6.83 (1H, s), 7.15 - 7.25 (2H, m), 7.30 (1H, d, J = 8.8 Hz), 7.70 - 7.80 (2H, m), 7.89 (1H, s)

Mass spectrum (ESI-MS, m/z): 374 (M⁺+1)

Example 308: N-(1H-5-Indazolyl)-N-(1-[(4-(trifluoromethyl)phenyl)sulfonyl]-3-piperidyl)amine

[0877] 4-Trifluorobenzenesulfonyl chloride (532 mg) was added dropwise to a solution (20 ml) of 3-hydroxypiperidine (200 mg) and triethylamine (0.33 ml) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give intermediate A.

[0878] This intermediate A and triethylamine (0.55 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0879] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction

mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (181.2 mg).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.40 - 1.44 (1H, m), 1.60 - 1.70 (2H, m), 2.36 (3H, s), 2.61 (1H, dd, J = 7.1, 11.5 Hz), 2.80 (1H, t, J = 8.5 Hz), 3.12 (1H, dd, J = 7.1, 8.5 Hz), 3.43 (1H, d, J = 11.5 Hz), 3.54 (1H, m), 6.75 (1H, dd, J = 2.0 Hz, 8.5 Hz), 6.78 (1H, s), 7.24 (2H, d, J = 8.5 Hz), 7.25 (1H, d, J = 8.3 Hz), 7.56 (2H, d, J = 8.3 Hz), 7.83 (1H, s)

Mass spectrum (ESI-MS, m/z): 424 (M⁺+1)

¹⁰ Example 309: N-(1H-5-Indazolyl)-N-[1-(phenylsulfonyl)-tetrahydro-1H-3-pyrrolyl]amine

[0880] Benzenesulfonyl chloride (0.2 ml) was added dropwise to a solution (20 ml) of (R)-(-)-3-pyrrolidinol hydrochloride (200 mg) and triethylamine (0.33 ml) in acetonitrile at room temperature, and the reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, water was poured into the reaction mixture, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give intermediate A.

[0881] This intermediate A and triethylamine (0.45 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (450.5 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0882] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (193.9 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (225.0 mg).

³⁰ ¹H-NMR (CDCl₃, 400 MHz): 1.75 - 1.82 (1H, m), 2.00 - 2.09 (1H, m), 3.15 - 3.27 (2H, m), 3.30 - 3.38 (1H, m), 3.43 (1H, dd, J = 5.6, 10.5 Hz), 3.85 - 3.88 (1H, m), 6.51 (1H, dd, J = 2.0, 8.8 Hz), 6.56 (1H, d, J = 1.5 Hz), 7.19 (1H, t, J = 3.9 Hz), 7.43 (2H, t, J = 7.6 Hz), 7.52 (1H, t, J = 7.3 Hz), 7.73 (2H, d, J = 7.6 Hz), 7.80 (1H, s)

Mass spectrum (ESI-MS, m/z): 342 (M⁺+1)

³⁵ Example 310: N-(1H-5-Indazolyl)-N-[1-[(4-methylphenyl)-sulfonyl]tetrahydro-1H-3-pyrrolyl]amine

[0883] p-Toluenesulfonyl chloride (308.5 mg) was added dropwise to a solution (20 ml) of (R)-(-)-3-pyrrolidinol hydrochloride (200 mg) and triethylamine (0.33 ml) in acetonitrile at room temperature, and the reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give intermediate A.

[0884] This intermediate A and triethylamine (0.45 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (450.5 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0885] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (193.9 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (125.9 mg).

⁵⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.85 - 1.91 (1H, m), 2.11 - 2.21 (1H, m), 2.46 (3H, s), 3.27 (1H, dd, J = 3.2, 10.7 Hz), 3.31 - 3.44 (2H, m), 3.52 (1H, dd, J = 5.6, 10.5 Hz), 3.96 - 4.02 (1H, m), 6.60 (1H, dd, J = 2.2, 8.8 Hz), 6.65 (1H, d, J = 2.0 Hz), 7.30 (1H, d, J = 10.7 Hz), 7.32 (2H, d, J = 10.5 Hz), 7.71 (2H, d, J = 8.3 Hz), 7.88 (1H, S)

Mass spectrum (ESI-MS, m/z): 355 (M⁺+1)

Example 311: N-[1-[(4-Chlorophenyl)sulfonyl]tetrahydro-1H-3-pyrrolyl]-N-(1H-5-indazolyl)amine

[0886] 4-Chlorobenzenesulfonyl chloride (341.6 mg) was added dropwise to a solution (20 ml) of (R)-(-)-3-pyrrolidinol hydrochloride (200 mg) and triethylamine (0.33 ml) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure to give intermediate A.

[0887] This intermediate A and triethylamine (0.45 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (450.5 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0888] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (193.9 mg), and the mixture was stirred at room temperature for 30 min, followed by dissolution in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (143.2 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.85 - 1.91 (1H, m), 2.11 - 2.21 (1H, m), 2.46 (3H, s), 3.27 (1H, dd, J = 3.2, 10.7 Hz), 3.31 - 3.44 (2H, m), 3.52 (1H, dd, J = 5.6, 10.5 Hz), 3.96 - 4.02 (1H, m), 6.60 (1H, dd, J = 2.2, 8.8 Hz), 6.65 (1H, d, J = 2.0 Hz), 7.30 (1H, d, J = 10.7 Hz), 7.32 (2H, d, J = 10.5 Hz), 7.71 (2H, d, J = 8.3 Hz), 7.88 (1H, s)

Mass spectrum (ESI-MS, m/z): 378 (M⁺+1)

Example 312: N-[1-(2,6-Dichlorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0889] 2,6-Dichlorobenzyl chloride (425.1 mg) was added dropwise to a solution (10 ml) of 3-hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0890] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0891] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (254.5 mg).

¹H-NMR (CD₃OD, 400 MHz): 1.70 - 1.82 (1H, m), 1.85 - 2.00 (1H, m), 2.10 - 2.18 (2H, m), 3.35 (1H, dt, J = 2.9, 12.2 Hz), 3.44 (1H, t, J = 11.2 Hz), 3.59 (1H, d, J = 12.2 Hz), 3.68 (1H, d, J = 10.0 Hz), 4.00 - 4.10 (1H, m), 4.69 (2H, s), 7.36 (1H, dd, J = 1.2, 8.8 Hz), 7.40 (1H, d, J = 6.6 Hz), 7.46 (1H, d, J = 2.0 Hz), 7.59 (1H, d, J = 9.0 Hz), 8.16 (1H, d, J = 0.7 Hz)

Mass spectrum (ESI-MS, m/z): 375 (M⁺+1)

Example 313: N-[1-(2,5-Dichlorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0892] 2,5-Dichlorobenzyl chloride (521.8 mg) was added dropwise to a solution (10 ml) of 3-hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0893] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (1 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer

was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0894] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (243.8 mg).

Mass spectrum (ESI-MS, m/z): 375 (M⁺+1)

Example 314: N-[1-(2,4-Dichlorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0895] 2,4-Dichlorobenzyl bromide (521.8 mg) was added dropwise to a solution (10 ml) of 3-hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0896] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0897] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added thereto, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (192.0 mg).

¹H-NMR (DMSO, 400 MHz): 1.70 - 1.80 (1H, m), 1.80 - 1.90 (1H, m), 2.00 - 2.20 (2H, m), 3.10 - 3.50 (3H, m), 3.61 (1H, d, J = 10.5 Hz), 4.00 - 4.10 (1H, m), 4.51 (2H, s), 7.35 (1H, dd, J = 2.0, 8.8 Hz), 7.41 (1H, dd, J = 2.0, 8.3 Hz), 7.51 (1H, d, J = 2.0 Hz), 7.63 (1H, dd, J = 4.9, 9.0 Hz), 7.72 (1H, d, J = 8.3 Hz), 8.21 (1H, s)

Mass spectrum (ESI-MS, m/z): 375 (M⁺+1)

Example 315: N-[1-(2,6-Difluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine

[0898] 2,6-Difluorobenzyl chloride (353.5 mg) was added dropwise to a solution (10 ml) of 3-hydroxypiperidine (200 mg) and potassium carbonate (327.8 mg) in acetonitrile at room temperature. The reaction mixture was stirred at room temperature for 18 hr and was then filtered through Celite, and the filtrate was concentrated to give intermediate A.

[0899] This intermediate A and triethylamine (0.50 ml) were dissolved in anhydrous dimethyl sulfoxide (10 ml), and a sulfur trioxide-trimethylamine complex (550.3 mg) was added to the solution in an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 18 hr. A saturated aqueous sodium hydrogen-carbonate solution (10 ml) was then added thereto, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and was concentrated to give intermediate B.

[0900] Titanium isopropoxide was added to this intermediate B and 5-aminoindazole (236.9 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (237.5 mg).

¹H-NMR (CD₃OD, 400 MHz): 1.45 - 1.52 (1H, m), 1.80 - 1.90 (1H, m), 1.95 - 2.05 (2H, m), 2.80 - 3.00 (1H, m), 3.00 - 3.05 (1H, m), 3.38 - 3.40 (1H, m), 3.50 - 3.55 (1H, m), 3.70 - 3.75 (1H, m), 4.40 (2H, s), 6.96 (1H, dd, J = 2.0, 7.3 Hz), 6.97 (1H, S), 7.07 (1H, t, J = 8.1 Hz), 7.35 (1H, dd, J = 1.0, 9.8 Hz), 7.48 - 7.55 (1H, m), 7.89 (1H, s)

Mass spectrum (ESI-MS, m/z): 342 (M⁺+1)

Example 316: N-(1H-5-Indazolyl)-N-[1-(2-propynyl)-4-piperidyl]amine

[0901] Propargyl bromide (0.19 ml), 4-piperidone monohydrate (300 mg), and potassium carbonate (539.8 mg) were dissolved in acetonitrile (10 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0902] Titanium isopropoxide was added to this intermediate and 5-aminoindazole (208.0 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (170.6 mg).

¹H-NMR (CDCl₃, 400 MHz): 1.55 (2H, dq, J = 3.7, 10.5 Hz), 2.13 (2H, d, J = 12.2 Hz), 2.26 (1H, t, J = 2.5 Hz), 2.41 (2H, dt, J = 2.5, 10.5 Hz), 2.89 (2H, d, J = 12.2 Hz), 3.28 - 3.35 (1H, m), 3.34 (2H, d, J = 2.4 Hz), 6.79 (1H, dd, J = 2.0, 8.5 Hz), 6.81 (1H, s), 7.28 (1H, d, J = 8.8 Hz), 7.86 (1H, d, J = 1.0 Hz)

Mass spectrum (ESI-MS, m/z): 254 (M⁺+1)

Example 317: N-(1-Butyl-3-piperidyl)-N-(1H-5-indazolyl)-amine

[0903] n-Butyl bromide (0.23 ml), 4-piperidone monohydrate (300 mg), and potassium carbonate (539.8 mg) were dissolved in acetonitrile (10 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0904] Titanium isopropoxide was added to this intermediate and 5-aminoindazole (208.0 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (99.6 mg).

¹H-NMR (CDCl₃, 400 MHz): 0.85 (3H, t, J = 7.3 Hz), 1.25 (2H, q, J = 7.3 Hz), 1.43 (4H, t, J = 8.1 Hz), 2.03 (2H, d, J = 9.3 Hz), 2.08 (2H, d, J = 11.2 Hz), 2.29 (2H, t, J = 7.3 Hz), 2.85 (2H, d, J = 8.6 Hz), 3.15 - 3.30 (1H, m), 6.72 (1H, dd, J = 2.0, 8.3 Hz), 6.74 (1H, s), 7.20 (1H, d, J = 8.3 Hz), 7.81 (1H, s)

Mass spectrum (ESI-MS, m/z): 272 (M⁺+1)

Example 318: N-(5-Isoquinolyl)-N-(1-propyl-4-piperidyl)-amine

[0905] n-Propyl bromide (0.2 ml), 4-piperidone monohydrate (300 mg), and potassium carbonate (539.8 mg) were dissolved in acetonitrile (10 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0906] Titanium isopropoxide was added to this intermediate and 5-aminoisoquinoline (208.0 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (101.3 mg).

¹H-NMR (CDCl₃, 400 MHz): 0.85 (3H, t, J = 7.3 Hz), 1.47 (2H, q, J = 7.6 Hz), 1.57 (2H, dq, J = 4.2, 10.7 Hz), 1.92 (1H, s), 2.05 - 2.18 (4H, m), 2.28 (2H, t, J = 7.8 Hz), 2.87 (2H, d, J = 12.2 Hz), 3.38 - 3.50 (1H, m), 4.19 (1H, d, J = 5.4 Hz), 6.71 (1H, d, J = 7.6 Hz), 7.22 (1H, d, J = 8.1 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.46 (1H, d, J = 6.1 Hz), 8.39 (1H, d, J = 5.9 Hz), 9.07 (1H, s)

Mass spectrum (ESI-MS, m/z): 269 (M⁺+1)

Example 319: N-(1-Isobutyl-4-piperidyl)-N-(5-isooquinolyl)amine

[0907] 1-Bromo-2-methylpropane (0.23 mg), 4-piperidone monohydrate (300 mg), and potassium carbonate (539.8

mg) were dissolved in acetonitrile (10 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0908] Titanium isopropoxide was added to this intermediate and 5-aminoisoquinoline (208.0 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (150.3 mg).

¹H-NMR (CDCl₃, 400 MHz): 0.84 (6H, d, J = 6.6 Hz), 1.56 (2H, dq, J = 3.2, 10.5 Hz), 1.68 - 1.77 (1H, m), 2.06 (4H, d, J = 7.3 Hz), 2.09 (2H, d, J = 10.7 Hz), 2.79 (2H, d, J = 11.9 Hz), 3.38 - 3.45 (1H, m), 6.70 (1H, d, J = 7.6 Hz), 7.21 (1H, d, J = 8.1 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.45 (1H, d, J = 5.9 Hz), 8.38 (1H, d, J = 5.9 Hz), 9.07 (1H, s)

Mass spectrum (ESI-MS, m/z): 283 (M⁺+1)

Example 320: N-[1-(2-Ethylbutyl)-4-piperidyl]-N-(5-isoquinolyl)amine

[0909] 1-Bromo-2-ethylbutane (0.3 ml), 4-piperidone monohydrate (300 mg), and potassium carbonate (539.8 mg) were dissolved in acetonitrile (10 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0910] Titanium isopropoxide was added to this intermediate and 5-aminoisoquinoline (208 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (203.8 mg).

¹H-NMR (CDCl₃, 400 MHz): 0.86 (6H, t, J = 7.3 Hz), 1.2 - 1.4 (5H, m), 1.60 (2H, q, J = 13.2 Hz), 2.10 (3H, t, J = 11.7 Hz), 2.15 (3H, d, J = 7.1 Hz), 2.82 (2H, d, J = 11.7 Hz), 3.18 - 3.22 (1H, m), 4.22 (1H, bs), 6.70 (1H, d, J = 7.6 Hz), 7.21 (1H, d, J = 8.3 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.45 (1H, d, J = 5.9 Hz), 8.38 (1H, d, J = 5.9 Hz), 9.07 (1H, s)

Mass spectrum (ESI-MS, m/z): 311 (M⁺+1)

Example 321: N-[1-(Cyclopropylmethyl)-4-piperidyl]-N-(5-isoquinolyl)amine

[0911] (Bromomethyl)cyclopropane (0.21 ml), 4-piperidone monohydrate (300 mg), and potassium carbonate (539.8 mg) were dissolved in acetonitrile (10 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0912] Titanium isopropoxide was added to this intermediate and 5-aminoisoquinoline (208 mg), and the mixture was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (183.5 mg).

¹H-NMR (CDCl₃, 400 MHz): 0.01 (2H, q, J = 5.1 Hz), 0.41 (1H, q, J = 2.4 Hz), 0.41 (1H, dd, J = 1.2, 8.1 Hz), 0.72 - 0.82 (1H, m), 1.59 (2H, dq, J = 3.7, 10.2 Hz), 2.06 (2H, dd, J = 2.4, 10.9 Hz), 2.16 (2H, d, J = 11.5 Hz), 2.21 (2H, d, J = 6.6 Hz), 2.97 (2H, d, J = 11.9 Hz), 3.35 - 3.41 (1H, m), 4.13 (1H, bs), 6.60 (1H, d, J = 7.3 Hz), 7.11 (1H, s), 7.14 (1H, d, J = 8.3 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.39 (1H, d, J = 5.9 Hz), 8.31 (1H, d, J = 5.9 Hz), 8.99 (1H, s)

Mass spectrum (ESI-MS, m/z): 281 (M⁺+1)

Example 322: N-[1-(3-Fluoropropyl)-4-piperidyl]-N-(5-isoquinolyl)amine

[0913] 1-Bromo-3-fluoropropane (86 mg), 4-piperidone monohydrate (300 mg), and potassium carbonate (539.8 mg) were dissolved in acetonitrile (10 ml), and the mixture was then stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite, and the filtrate was then concentrated to give an intermediate.

[0914] Titanium isopropoxide was added to this intermediate and 5-aminoisoquinoline (225.3 mg), and the mixture

was stirred at room temperature for 30 min. Thereafter, the reaction mixture was dissolved in methanol. Sodium borohydride was added to the solution, and the mixture was stirred at room temperature for 3 hr. After the completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was then concentrated. Water was poured into the concentrate, and the mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over sodium sulfate. The solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography [silica gel, chloroform-methanol] to give the title compound (210.9 mg).

⁵ ¹H-NMR (CDCl₃, 400 MHz): 1.56 (2H, dq, J = 4.2, 9.8 Hz), 1.82 (1H, dq, J = 1.5, 7.1 Hz), 1.88 (1H, dq, J = 1.5, 7.1 Hz), 2.10 (2H, d, J = 11.2 Hz), 2.45 (2H, t, J = 7.6 Hz), 2.48 - 2.55 (1H, m), 2.85 (2H, d, J = 11.7 Hz), 3.43 (1H, s), 4.22 (1H, s), 4.39 (1H, t, J = 6.1 Hz), 4.50 (1H, t, J = 5.9 Hz), 6.69 (1H, d, J = 7.56 Hz), 7.21 (1H, d, J = 8.1 Hz), 7.36 (1H, t, J = 8.1 Hz), 7.46 (1H, d, J = 5.9 Hz), 8.37 (1H, d, J = 6.1 Hz), 9.1 (1H, s)

¹⁰ Mass spectrum (ESI-MS, m/z): 287 (M⁺+1)

[0915] The compounds prepared in the above examples had the following structures.

15

20

25

30

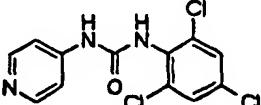
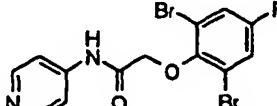
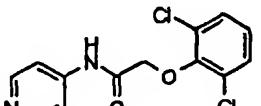
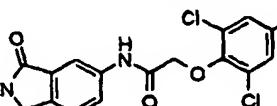
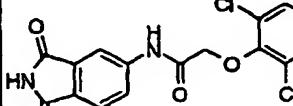
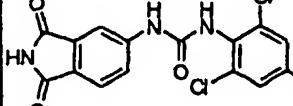
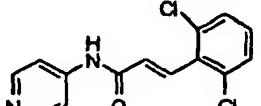
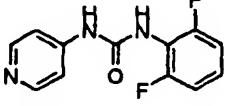
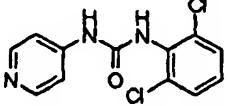
35

40

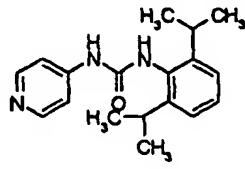
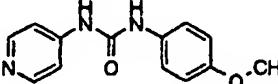
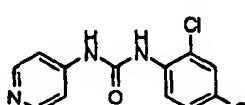
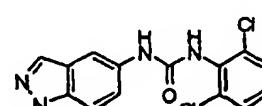
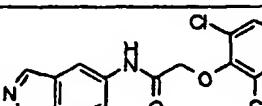
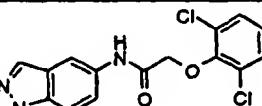
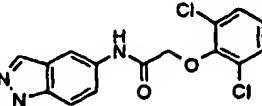
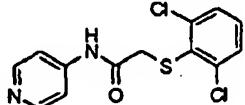
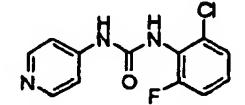
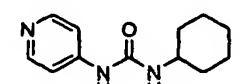
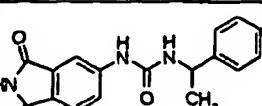
45

50

55

Ex. No.	Structural formula	IC50 (μM)
5	1	 0.2
10	2	 2.21
15	3	 0.91
20	4	
25	5	
30	6	
35	7	 2.54
40	8	 2
45	9	 0.85
50		

5

		
10		
11		
12		0.98
13		1.14
14		0.46
15		
16		9.6
17		2.87
18		7.26
19		0.11
20		

10

15

20

25

30

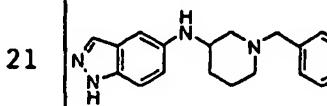
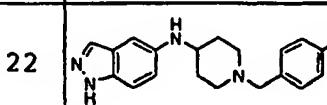
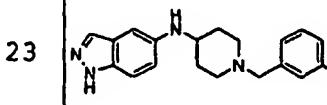
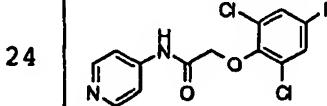
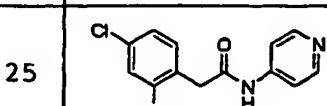
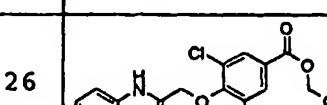
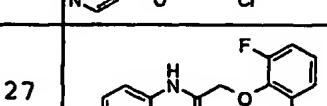
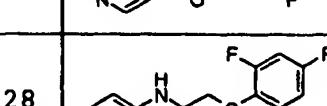
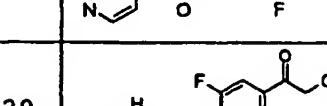
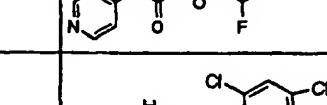
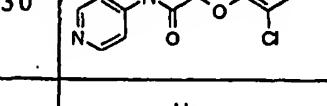
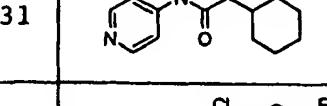
35

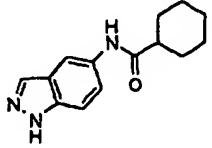
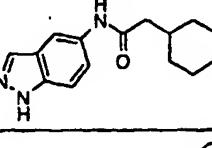
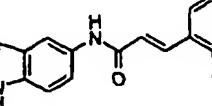
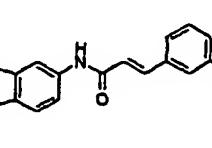
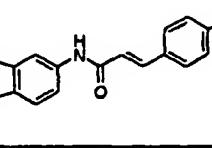
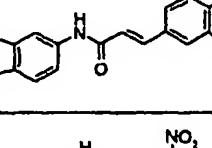
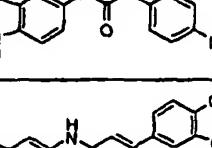
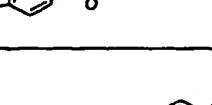
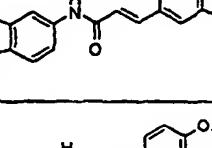
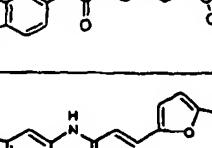
40

45

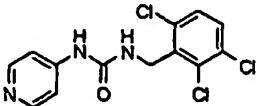
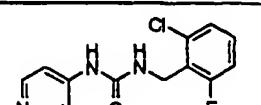
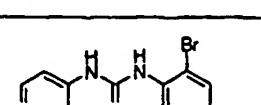
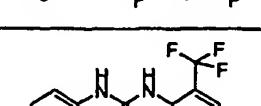
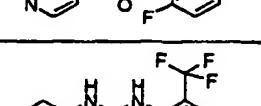
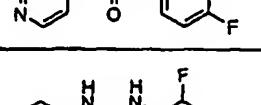
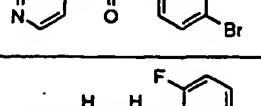
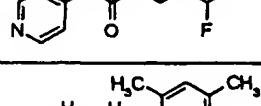
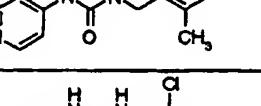
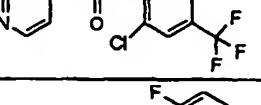
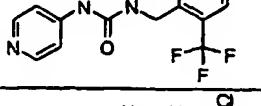
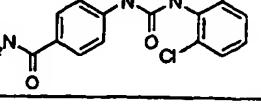
50

55

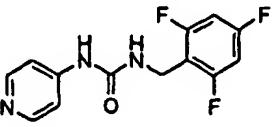
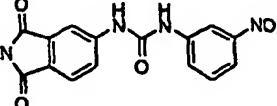
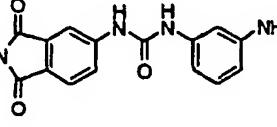
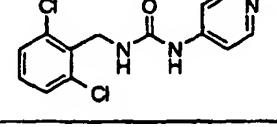
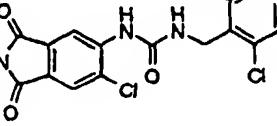
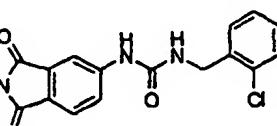
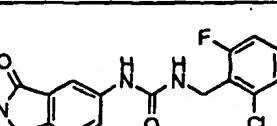
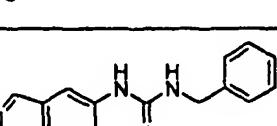
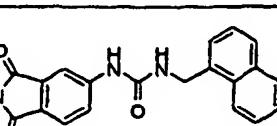
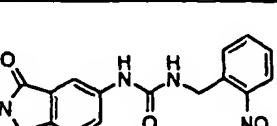
5	21		0.02
10	22		
15	23		0.124
20	24		0.48
25	25		
30	26		1.03
35	27		
40	28		8.11
45	29		8.59
50	30		1.15
55	31		5.29
	32		1.37

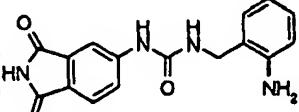
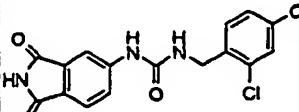
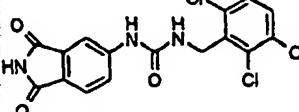
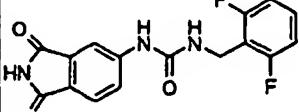
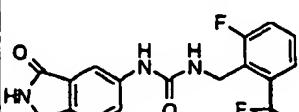
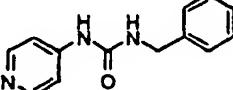
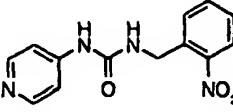
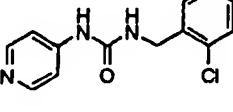
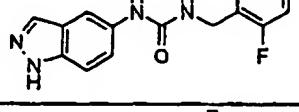
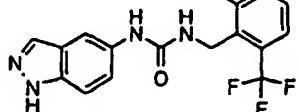
5	33		0.47
10	34		0.87
15	35		1.28
20	36		0.6
25	37		0.305
30	38		0.107
35	39		0.122
40	40		0.231
45	41		0.224
50	42		0.605
55	43		0.723

5	44		0.394
10	45		0.153
15	46		0.57
20	47		0.735
25	48		0.191
30	49		0.513
35	50		0.326
40	51		0.459
45	52		0.23
50	53		4.14
55	54		

5	55 	1.04
10	56 	
15	57 	1.11
20	58 	13.55
25	59 	7.27
30	60 	10.97
35	61 	6.95
40	62 	
45	63 	2.5
50	64 	2.19
55	65 	9
	66 	6.57

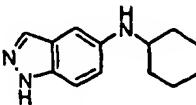
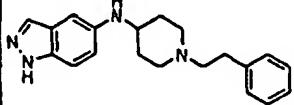
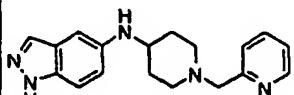
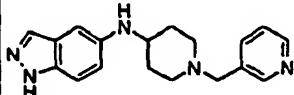
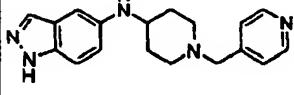
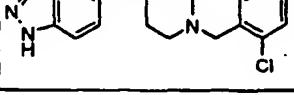
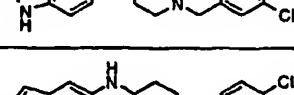
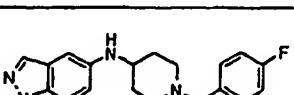
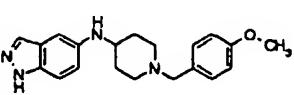
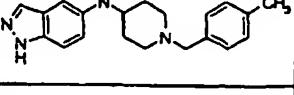
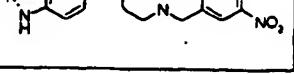
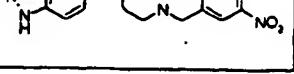
5	67		1.92
10	68		0.11
15	69		2.27
20	70		0.4
25	71		3.12
30	72		0.9
35	73		0.41
40	74		8.3
45	75		6.03
50	76		1.69
55			

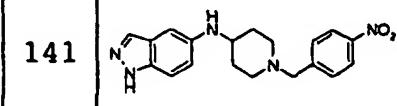
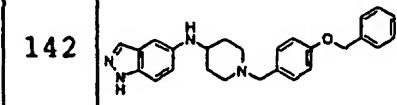
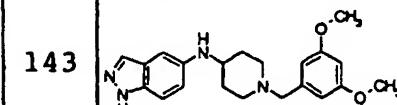
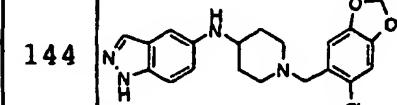
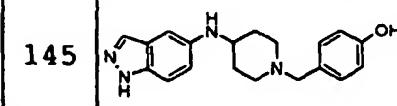
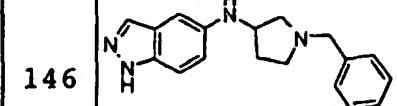
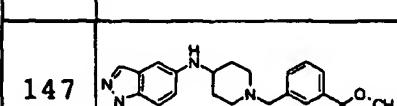
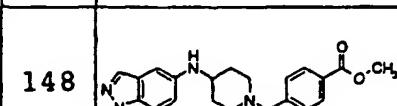
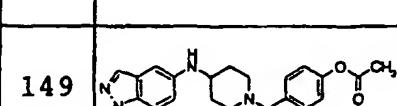
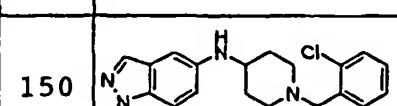
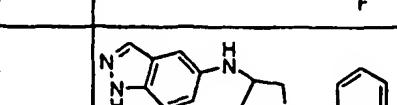
5	77		4.07
10	78		10.41
15	79		8.57
20	80		0.77
25	81		0.054
30	82		0.29
35	83		0.06
40	84		0.26
45	85		0.18
50	86		0.9
55			

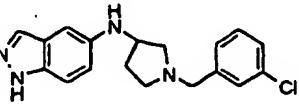
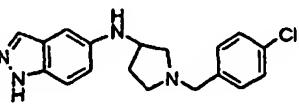
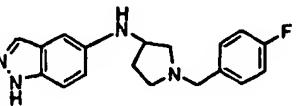
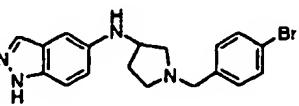
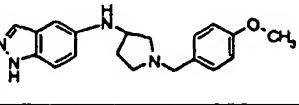
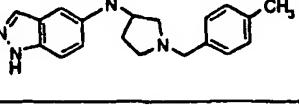
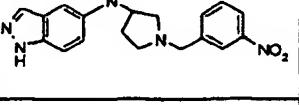
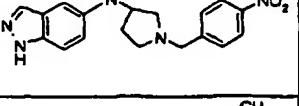
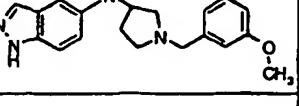
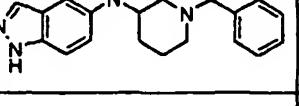
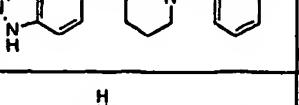
5	87		0.18
10	88		0.44
15	89		0.3
20	90		0.069
25	91		0.099
30	92		10.2
35	93		12.5
40	94		7.2
45	95		0.085
50	96		0.23

5	97		2.1
10	98		0.41
15	99		0.24
20	100		0.22
25	101		1.8
30	102		0.079
35	103		0.26
40	104		0.24
45	105		0.39
50	106		1.4

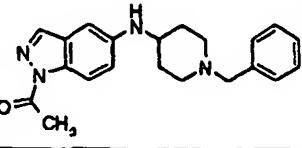
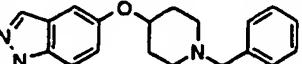
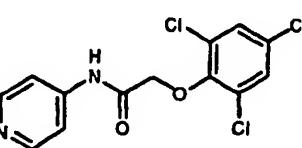
5	118		0.275
10	119		0.383
15	120		0.241
20	121		0.513
25	122		0.309
30	123		0.22
35	124		0.238
40	125		0.747
45	126		0.239
50	127		0.951
55	128		0.287

5	129		0.67
10	130		0.457
15	131		
20	132		0.603
25	133		0.68
30	134		0.436
35	135		0.285
40	136		
45	137		0.478
50	138		0.355
55	139		0.25
	140		0.465

5	141		0.661
10	142		0.655
15	143		0.399
20	144		0.453
25	145		0.29
30	146		0.032
35	147		0.462
40	148		0.166
45	149		0.204
50	150		0.821
55	151		0.045

5	152		0.02
10	153		0.024
15	154		0.084
20	155		0.024
25	156		0.002
30	157		0.022
35	158		0.005
40	159		0.012
45	160		0.001
50	161		0.013
55	162		0.019
	163		0.011

5	164		0.016
10	165		0.011
15	166		0.016
20	167		0.009
25	168		0.003
30	169		0.087
35	170		0.08
40	171		0.09
45	172		0.265
50	173		0.446
55	174		0.163
	175		15.557

5	176		0.004
10	177		
15	178		

20

25

30

35

40

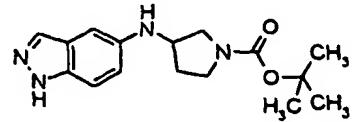
45

50

55

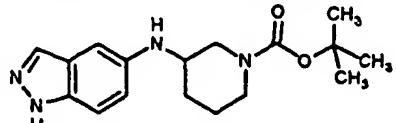
5

179



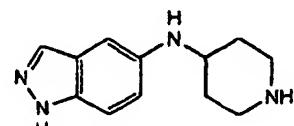
10

180

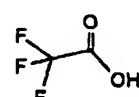


15

181

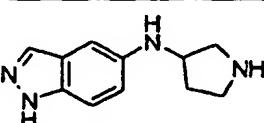


20

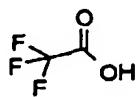


25

182

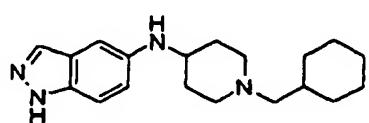


30



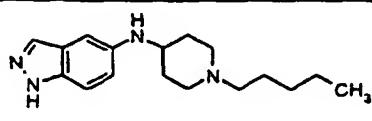
35

183



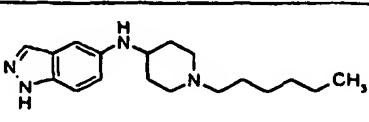
40

184



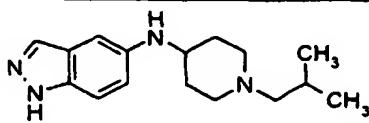
45

185

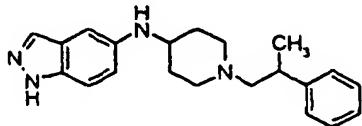
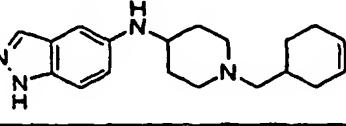
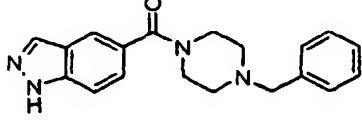
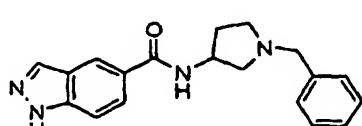
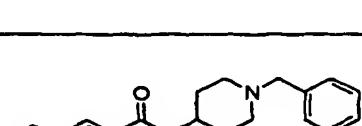
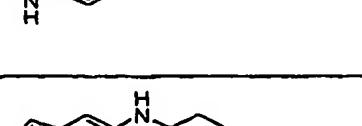
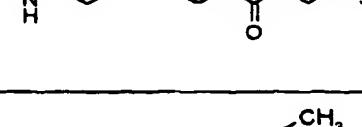
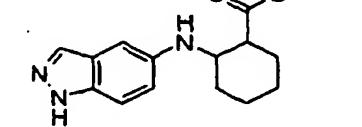


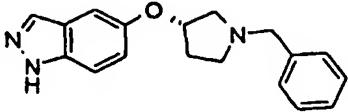
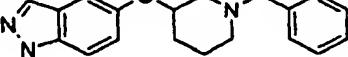
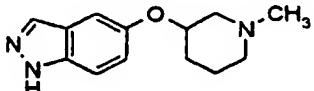
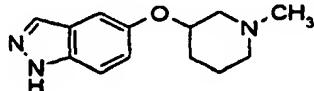
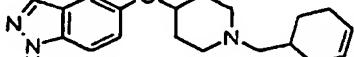
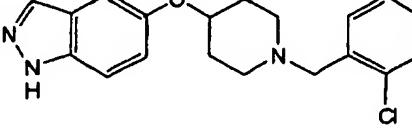
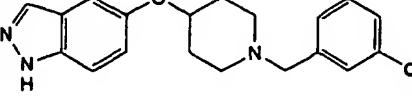
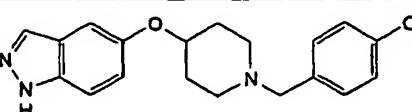
50

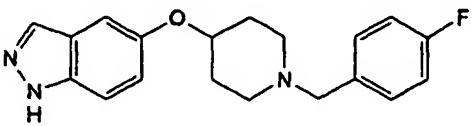
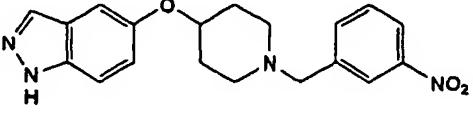
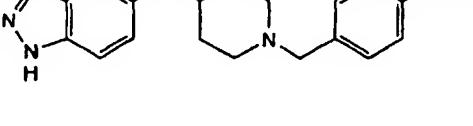
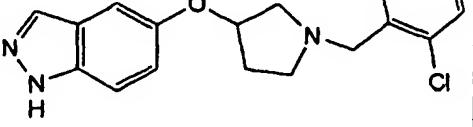
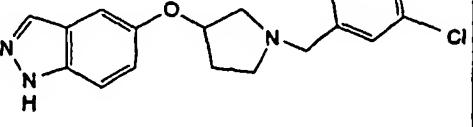
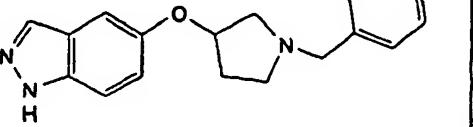
186

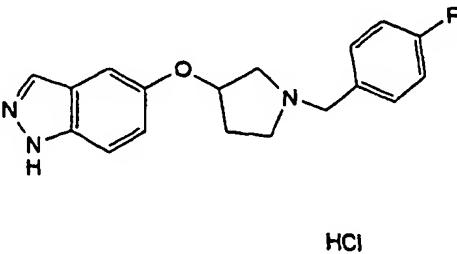
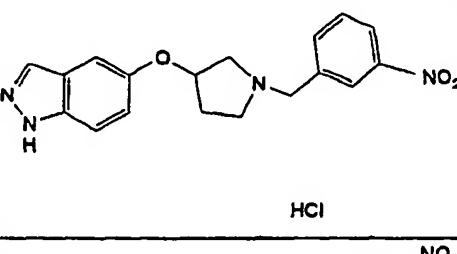
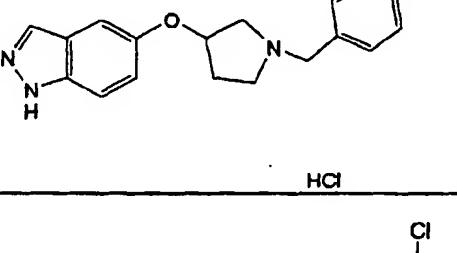
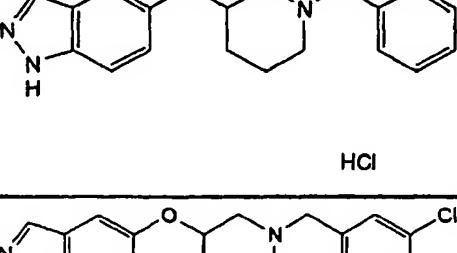
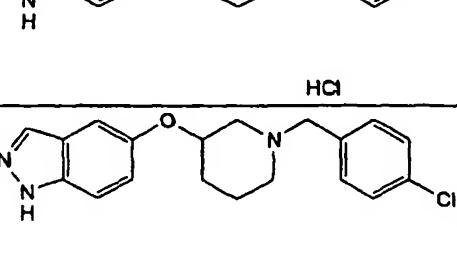
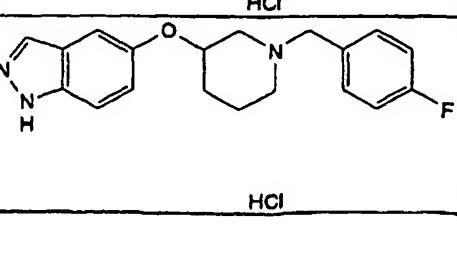


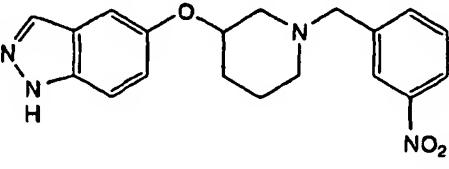
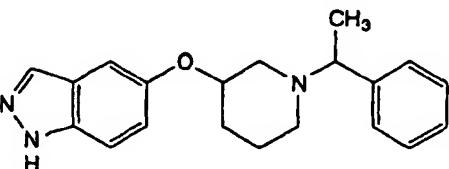
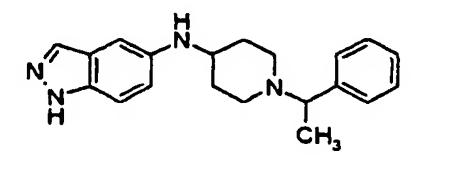
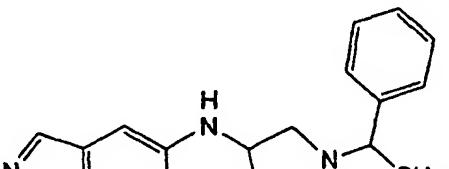
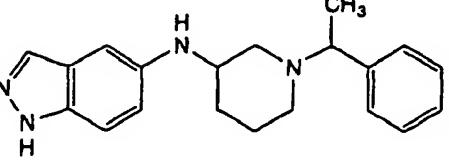
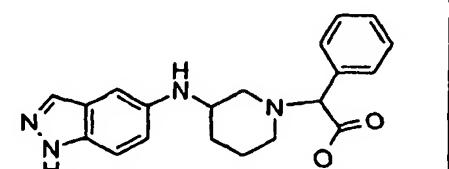
55

5	187			
10	188			
15	189			
20	190			
25	191			
30	192			
35	193			
40	194			
45				
50				

5	195			
10	196			
15	197			
20	198			
25	199			
30	200		HCl	
35	201		HCl	
40	202		HCl	
45				
50				

5	203		HCl	
10	204		HCl	
15	205		HCl	
20	206		HCl	
25	207		HCl	
30	208		HCl	
35				
40				
45				
50				
55				

5	209	 HCl	
10	210	 HCl	
15	211	 HCl	
20	212	 HCl	
25	213	 HCl	
30	214	 HCl	
35	215	 HCl	
40			
45			
50			
55			

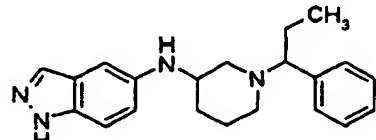
5	216	 HCl	
10	217	 HCl	
15	218		
20	219	 HCl	
25	220	 HCl	
30	221		
35			
40			
45			
50			
55			

5	222		
10	223		
15	224		
20	225		
25	226		
30	227		
35	228		
40			
45			
50			
55			

5	229		
10	230		
15	231		
20	232		
25	233		
30	234		
35	235		
40			
45			
50			
55			

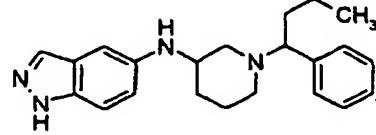
5

236



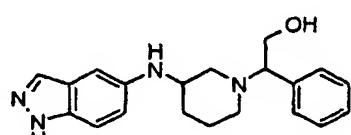
10

237



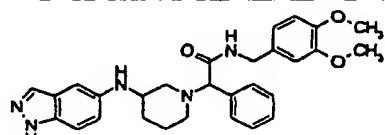
15

238



20

239



25

240

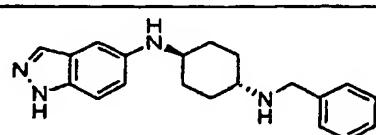


30

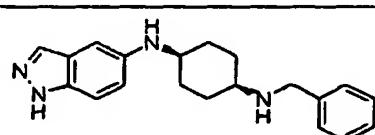
35

241

anti



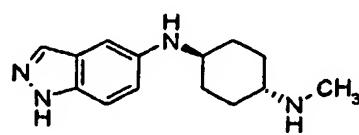
syn



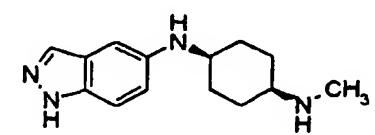
40

242

anti



syn

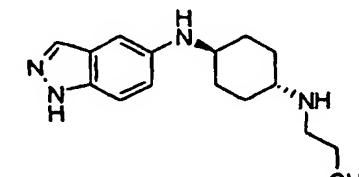


45

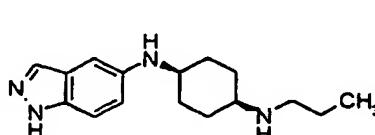
50

243

anti

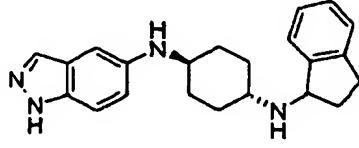
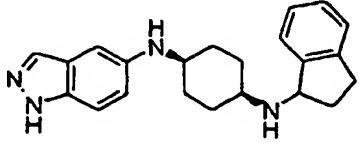
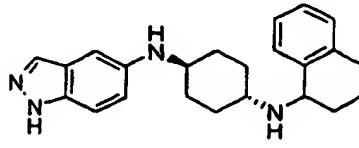
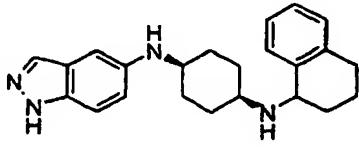
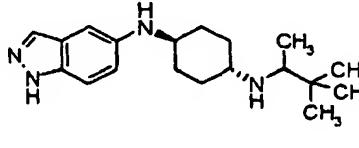
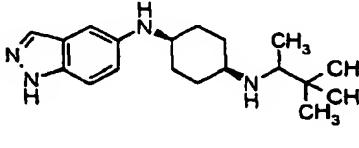
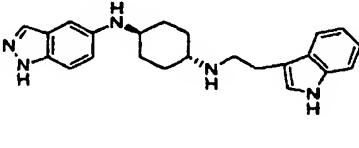
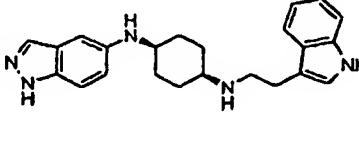
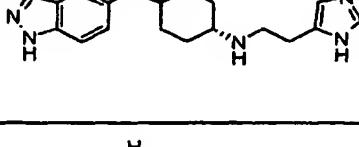
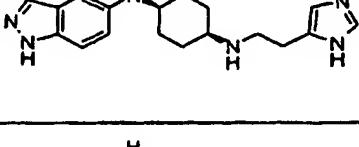
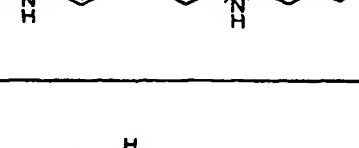
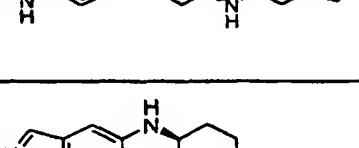
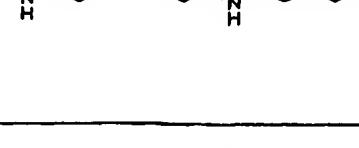
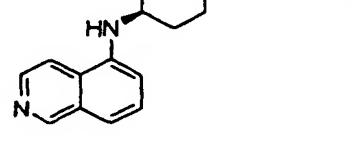
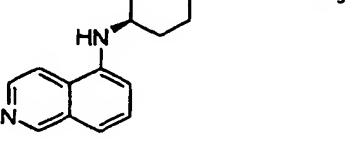


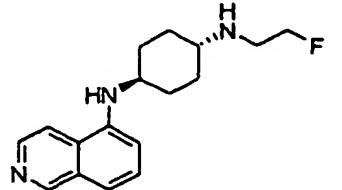
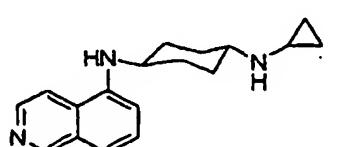
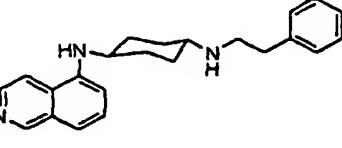
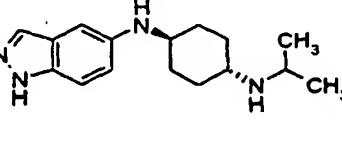
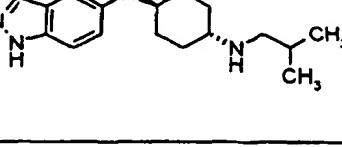
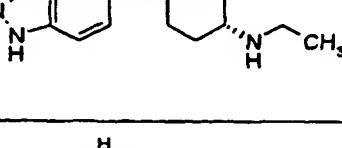
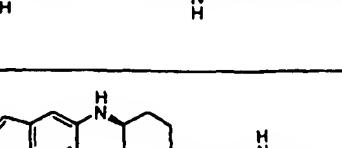
syn

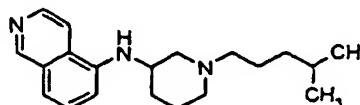
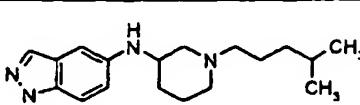
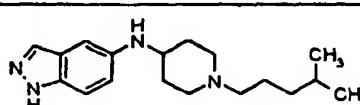
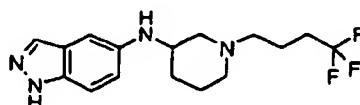
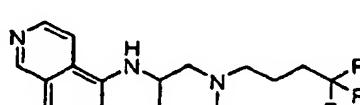
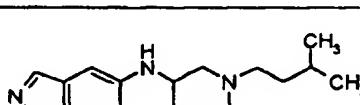
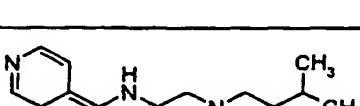
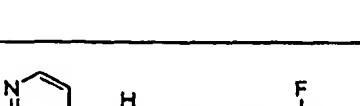
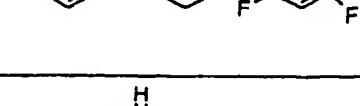


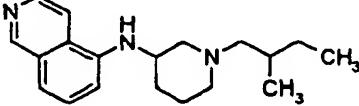
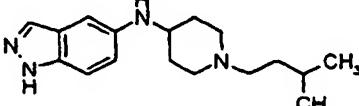
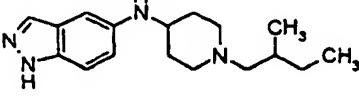
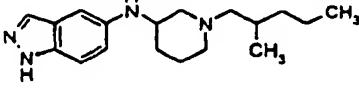
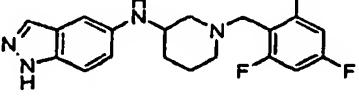
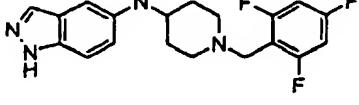
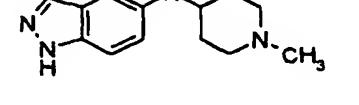
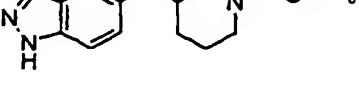
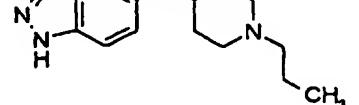
55

5	244	anti		syn	
10	245	anti		syn	
15	246	anti		syn	
20	247	anti		syn	
25	248	anti		syn	
30	249	anti		syn	
35	250	anti		syn	
40	251	anti		syn	
45	252	anti		syn	
50					
55					

5	253	anti		syn	
10	254	anti		syn	
15	255	anti		syn	
20	256	anti		syn	
25	257	anti		syn	
30	258	anti		syn	
35	259	anti		syn	
40	260	anti		syn	
45					
50					
55					

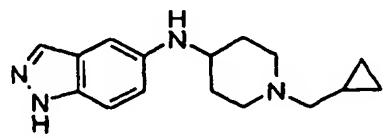
5	261	anti		syn
10	262	anti		syn
15	263	anti		syn
20	264	anti		syn
25	265	anti		syn
30	266	anti		syn
35	267	anti		syn
40	268	anti		syn
45				
50				
55				

5	269			
10	270			
15	271			
20	272			
25	273			
30	274			
35	275			
40	276			
45	277			
50				

5	278			
10	279			
15	280			
20	281			
25	282			
30	283			
35	284			
40	285			
45	286			
50				
55				

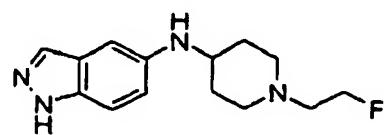
5

287



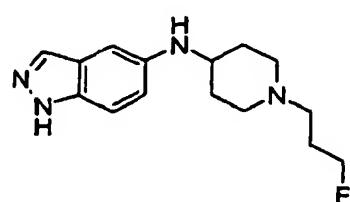
10

288



15

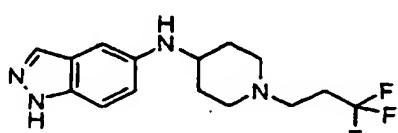
289



20

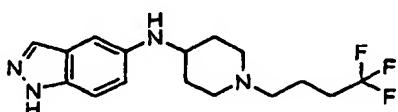
25

290



30

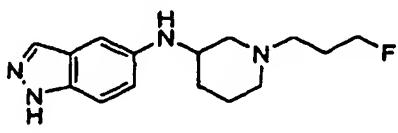
291



35

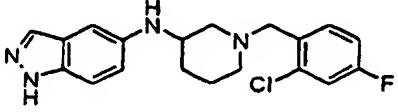
40

292



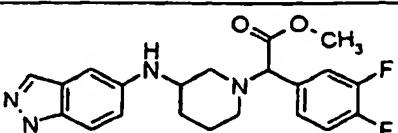
45

293

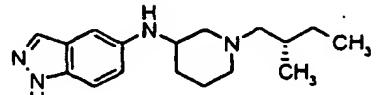
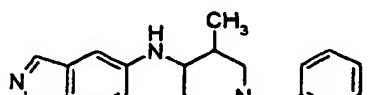
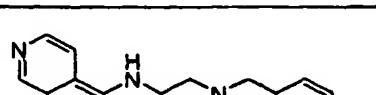
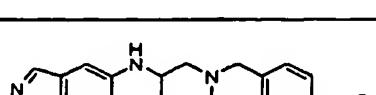
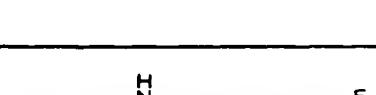
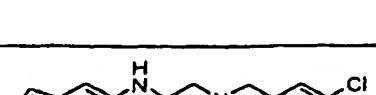


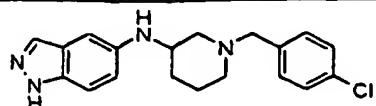
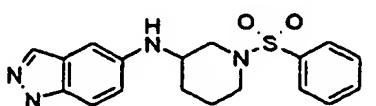
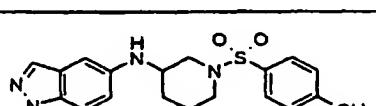
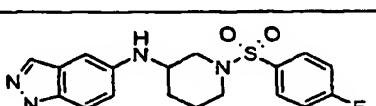
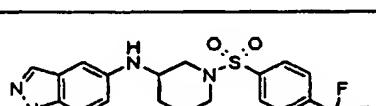
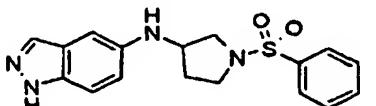
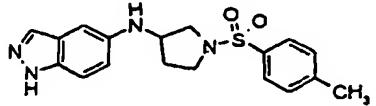
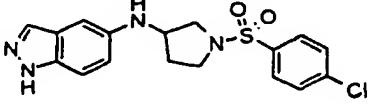
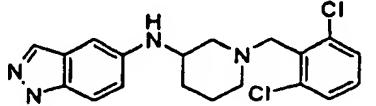
50

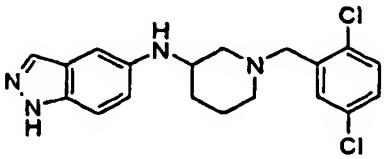
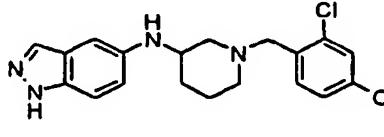
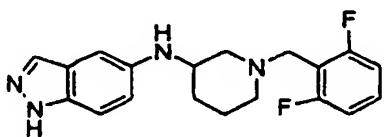
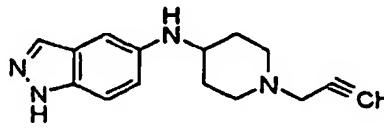
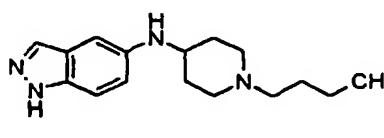
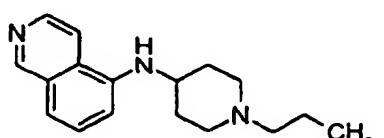
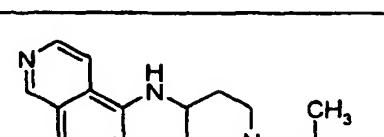
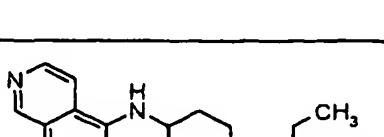
294

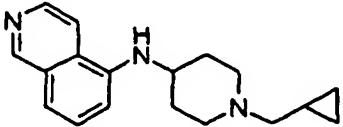
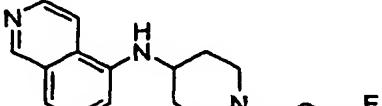


55

5	295			
10	296			
15	297			
20	298			
25	299			
30	300			
35	301			
40	302			
45	303			
50				
55				

5	304			
10	305			
15	306			
20	307			
25	308			
30	309			
35	310			
40	311			
45	312			
50				

5	313			
10	314			
15	315			
20	316			
25	317			
30	318			
35	319			
40	320			
45				
50				
55				

5	321			
10	322			
15				

20 Pharmacological Test Example 1: Rho kinase inhibitory activity

[0916] Gene recombinant Rho kinase was prepared according to the disclosure of Japanese Patent Laid-Open No. 113187/1998, i.e., by infecting insect cells with baculovirus, into which cDNA coding fused protein composed of bovine Rho kinase catalyst region and glutathione S-transferase had been incorporated, and allowing the insect cells to produce the gene recombinant Rho kinase. A substrate (ribosomal S6 kinase substrate, S6 231-239) was phosphorylated by adding the Rho kinase, together with ATP ($\gamma^{32}\text{P}$ -ATP) of which phosphorus at the γ -position had been labeled with a radioisotope, to the substrate. This permits the substrate to be labeled with the radioisotope.

[0917] Thereafter, the substrate was adsorbed to a filter paper. ATP was washed away with a phosphoric acid solution, and the amount of the phosphorylated substrate was then measured with a liquid scintillation counter.

[0918] The antienzymatic activity of a test compound was determined by adding the test sample before the enzymatic reaction, determining the percentage phosphorylation inhibition of the substrate, and determining as IC_{50} the concentration of the test compound necessary for inhibiting the phosphorylation by 50%.

[0919] The results were shown in the table described above.

35 Pharmacological Test Example 2: Leukocyte migration inhibitory activity

[0920] Human-derived histiocyte lymphoma (U937/CCR2), in which mouse-derived CCR2 had been highly expressed, was suspended in a 0.1% BSA-containing RPMI 1640 medium, to which a test compound had been added (5×10^6 /ml), and the suspension was incubated for 20 min. A chemical solution (500 μl) (0.1% BSA-containing RPMI 1640 medium DMSO 1%), to which an MCP-1 ligand (1 μM) and the test compound had been added, was added to a 24-well plate. CHEMOTAXICELL was put thereon, and 200 μl of the cell suspension was added to the top layer, followed by migration under 5% carbon dioxide at 37°C for one hr. The number of cells, which had migrated to the lower chamber, was counted with a particle count analyzer (CDA-500, SYSMEX CORPORATION), and the percentage migration inhibition was calculated by the following equation;

[0921] Migration inhibition (%) = {1 - (number of migrated cells in the presence of test compound/number of migrated cells in the absence of test compound)} \times 100

[0922] The results are shown in table below.

	Test compound (Ex. No.)	Migration inhibition (%) \pm SEM
50	20 (3 μM)	46.7 \pm 19.4
	20 (30 μM)	95.4 \pm 3.4
	21·HCl (3 μM)	83.5 \pm 3.3
	21·HCl (30 μM)	99.1 \pm 0.4
55	22 (3 μM)	34.8 \pm 12.4
	22 (30 μM)	92.9 \pm 1.3
	80 (3 μM)	26.0 \pm 4.7

(continued)

	Test compound (Ex. No.)	Migration inhibition (%) ± SEM
5	80 (30 µM)	65.1 ± 17.3
	83 (3 µM)	16.1 ± 9.6
	83 (30 µM)	92.5 ± 3.3
	90 (30 µM)	78.3 ± 3.2
10	95 (3 µM)	17.1 ± 11.7
	95 (30 µM)	77.6 ± 6.4
	102 (3 µM)	6.8 ± 17.0
	102 (30 µM)	96.7 ± 1.0
15	126 (30 µM)	49.1 ± 4.6
	126-HCl (3 µM)	9.9 ± 14.2
	126-HCl(30 µM)	41.6 ± 4.8
	128 (3 µM)	2.9 ± 12.3
20	128 (30 µM)	45.9 ± 12.3
	146 (3 µM)	45.6 ± 9.5
	146 (30 µM)	93.9 ± 1.7
	146-HCl (3 µM)	74.5 ± 1.7
25	146-HCl (30 µM)	97.9 ± 1.0
	221 (0.3 µM)	90.8 ± 11.0
	221 (0.03 µM)	27.5 ± 33.6
	298 (0.3 µM)	15.7 ± 9.9
30	300 (0.3 µM)	81.9 ± 11.9
	246 (0.3 µM)	41.9 ± 15.4
	243 (3 µM)	82.8 ± 7.1
	227 (3 µM)	100.3 ± 0.5
35	259 (syn) (3 µM)	85.3 ± 8.5
	293 (3 µM)	93.5 ± 9.9
	281 (3 µM)	100.1 ± 8.2
	294 (0.3 µM)	98.3 ± 1.4
40	294 (0.1 µM)	87.4 ± 6.4
	282 (1 µM)	29.9 ± 4.1
	260 (anti) (1 µM)	77.4 ± 14.4
	262 (anti) (1 µM)	82.5 ± 6.69
45	262 (anti) (0.3 µM)	24.4 ± 8.1
	260 (syn) (1 µM)	56.5 ± 14.9
	261 (syn) (1 µM)	59.4 ± 10.4
	261 (syn) (0.3 µM)	24.2 ± 3.9
	262 (syn) (1 µM)	69.9 ± 15.1
	320 (1 µM)	82.9 ± 7.0

Pharmacological Test Example 3: Albuminuria amelioration activity for anti-GBM nephritis model using S.D. rats

[0923] Anti-GBM antibody produced by immunizing domestic rabbits with a rat-derived GBM fraction was caudointravenously administered to S.D. male rats of 8 weeks old to induce nephritis. Immediately after the administration of the antibody and six hr after the administration of the antibody, the compound of Example 300 was orally administered at 30 mg/kg. Urine was collected in a period between immediately after the administration of the antibody and 24 hr after the administration of the antibody, and the protein level of urine was measured to observe albuminuria amelioration activity. The results are shown in the following table.

Group	Protein level of urine (mg/kg/day) ± SEM
Control group	794.2 ± 113.2
Group of oral administration of the compound of Example 300 at 30 mg/kg twice daily	437.1 ± 95.9

Pharmacological Test Example 4: Albuminuria amelioration activity for anti-GBM nephritis model using WKY rats

[0924] Anti-GBM antibody produced by immunizing domestic rabbits with a rat-derived GBM fraction was caudointravenously administered to WKY male rats of 9 weeks old to induce nephritis. For two weeks from the day after the administration of the antibody, the compound of Example 300 was orally administered at 30 mg/kg twice daily, and the compound prepared in Example 246 was administered at 25 mg/ml together with drinking water. During 24 hr from two weeks after the administration of the antibody, urine was collected, and the protein level of urine was measured to observe albuminuria amelioration activity. The results are shown in the following table.

Group	Protein level of urine (mg/kg/day) ± SEM
Control group	840.4 ± 82.2
Group of oral administration of the compound of Example 300 at 30 mg/kg twice daily	602.2 ± 47.3
Group of administration of the compound of Example 246 at 25 mg/liter together with drinking water	220.2 ± 17.7

Pharmacological Test Example 5: Antihypertensive activity

[0925] This pharmacological test example demonstrates that the compounds according to the present invention have antihypertensive activity in spontaneously hypertensive male rats (SHR, Charles River Japan, Inc.) of 11 to 18 weeks old by forced oral administration of the compounds. This test was carried out as follows. A test compound was dissolved in purified water, or alternatively the test compound was suspended in a 5% aqueous sodium carboxymethylcellulose solution. The solution or the suspension was forcibly administered into the gaster of SHR through an oral probe. The systolic pressure of SHR was measured with a bloodless sphygmometer (BP-98A, Softron Co.) immediately before the administration of the test compound and 3 to 4 hr after the administration of the test compound or 6 to 7 hr after the administration of the test compound. The percentage of blood pressure depression was calculated by the following equation:

Antihypertensive activity (%) = $\frac{\text{blood pressure}_1 - \text{blood pressure}_2}{\text{blood pressure}_1} \times 100$

before administration of test compound - blood pressure

after administration of test compound)/blood pressure

before administration of test compound} x 100

before administration of test compound} x 100

before administration of test compound} x 100

[0926] The results were as shown in the following table. Each compound was administered at 30 mg/kg, and the antihypertensive activity (%) was expressed in terms of the mean value of 3 to 4 SHRs and SEM (standard error of the mean).

[0927] For data with *, the blood pressure was measured 6 to 7 hr after the administration of the test compound, and, for data with no marks, the blood pressure was measured 3 to 4 hr after the administration of the test compound. The results are shown in the following table.

Test compound	Blood pressure depression, %
Example 126	18.0 ± 3.5
Example 127	20.4 ± 3.0
Example 21	37.0 ± 2.5

(continued)

	Test compound	Blood pressure depression, %
5	Example 164	35.0 ± 4.7
	Example 298	18.9 ± 3.1 *
	Example 300	24.1 ± 3.8 *
10	Example 227	22.2 ± 7.4
	Example 243 (syn)	20.4 ± 5.2
	Example 246 (syn)	37.2 ± 11.7
	Example 247 (syn)	43.3 ± 1.2
	Example 289	30.8 ± 5.7
15	Example 248 (anti)	18.8 ± 8.0
	Example 243 (syn)	26.4 ± 5.0
	Example 287	24.4 ± 6.8
	Example 286	23.6 ± 8.6
	Example 290	17.2 ± 2.9
20	Example 240	21.1 ± 6.5
	Example 261 (anti)	47.3 ± 3.6
	Example 261 (syn)	46.4 ± 4.8
	Example 260 (syn)	19.6 ± 10.5
	Example 322	41.4 ± 7.4
25	Example 318	22.7 ± 5.1
	Example 246 (anti)	51.4 ± 0.9
	Example 273	30.4 ± 7.3

Claims

- 30 1. A compound represented by formula (I) or a pharmaceutically acceptable salt or solvate thereof:

Het-X-Z

(I)

35 wherein

Het represents a five- to seven-membered monocyclic saturated or unsaturated heterocyclic group containing at least one nitrogen atom, or a nine- to twelve-membered bicyclic saturated or unsaturated heterocyclic group containing at least one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by a halogen atom, an oxygen atom, hydroxyl, or C₁₋₄ alkylcarbonyl,

40 X represents a group selected from the group consisting of groups (i) to (ix):

(i) -NH-C(=O)-NH-Q1-

45 wherein

Q1 represents

a bond,

alkylene having 1 to 4 carbon atoms, or

50 alkenylene having 2 to 4 carbon atoms, wherein the alkylenes and alkenylenes are optionally substituted by C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

(ii) -NH-C(=O)-Q2-

wherein

5 Q2 represents
 a bond,
 alkylene having 1 to 5 carbon atoms, or
 alkenylene having 2 to 5 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by
 C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally
 10 substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom;
 C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of
 which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion
 is optionally substituted by a halogen atom; or benzyloxy,

15 (iii) -NH-C(=O)-Q3-Q4-Q5-

wherein

20 Q3 represents
 alkylene having 1 to 4 carbon atoms or
 alkenylene having 2 to 4 carbon atoms,
 Q4 represents -O-, -NH-, or -S(=O)m- wherein m is an integer of 0 to 2,
 Q5 represents
 a bond,
 25 alkylene having 1 to 3 carbon atoms, or
 alkenylene having 2 or 3 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by
 C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally
 substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom;
 30 C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of
 which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion
 is optionally substituted by a halogen atom; or benzyloxy,

(iv) -N(-R¹)-Q6-Q7-

35 wherein

R¹ represents a hydrogen atom or C₁₋₄ alkyl carbonyl,
 Q6 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic
 40 group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄
 alkyl,
 Q7 represents
 a bond,

45 -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2-

wherein

n1 and n2 are each an integer of 0 to 3,
 when n2 is 2 or 3, -CH₂-CH₂- in -(CH₂)n2- may represent -CH=CH- or -C≡C-,
 50 R^{2a} and R^{2b}, which may be the same or different, represent
 a hydrogen atom,
 a halogen atom,
 C₁₋₆ alkyl optionally substituted by hydroxyl,
 carboxyl,
 55 C₁₋₄ alkoxy carbonyl,
 cyano,
 -(C=O)-N(-R^{2c})(-R^{2d}) wherein R^{2c} and R^{2d}, which may be the same or different, represent a hydrogen atom;
 C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy optionally substituted by a halogen atom; cyclo-

propyl; or benzyl of which the phenyl portion is optionally substituted by one or two C₁₋₄ alkoxys, or phenyl optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

-(CH₂)^p-NR³- wherein p is an integer of 0 to 2, R³ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

-NH-(CH₂)^{q1}-CR^{4a}R^{4b}-(CH₂)^{q2}- wherein q1 and q2 are each an integer of 0 to 2 and R^{4a} and R^{4b} each independently represent a hydrogen atom, C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

-(C=O)-O-CR^{4a}R^{4b}-CH₂- wherein R^{4a} and R^{4b} are as defined above,

-NH-(CH₂)ⁱ-NH- wherein i is an integer of 1 to 4, or

-S(=O)^j- wherein j is 0, 1, or 2,

(v) -NH-Q8-Q9-Q10-

wherein

Q8 represents

alkylene having 1 to 5 carbon atoms or
alkenylene having 2 to 5 carbon atoms,

Q9 represents -O-, -NH-, or -S(=O)r- wherein r is an integer of 0 to 2,

Q10 represents

a bond,

alkylene having 1 to 3 carbon atoms, or

alkenylene having 2 or 3 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or phenyl optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

wherein

Q11 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

Q12 represents

a bond,

-(CH₂)^s-CHR⁵- wherein s is an integer of 0 to 2 and R⁵ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

-(CH₂)^t-NR⁶- wherein t is an integer of 0 to 2 and R⁶ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom;

which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy, or

-NH-(CH₂)_u-CHR⁷- wherein u is an integer of 0 or 1 and R⁷ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

(vii)-Q13-Q14-

wherein

Q13 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

Q14 represents

a bond,

-(CH₂)_v-CHR⁸- wherein v represents an integer of 0 to 2 and R⁸ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

-(CH₂)_w-NR⁹- wherein w represents an integer of 0 to 2 and R⁹ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy, or

-NH-(CH₂)_x-CHR¹⁰- wherein x is an integer of 0 or 1 and R¹⁰ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

(viii) -C(=O)-Q15-(CH₂)_y-

wherein Q15 represents a five- to seven-membered saturated or unsaturated heterocyclic group and this heterocyclic group is optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl and y is an integer of 0 to 4, and

(ix) -C(=O)-NR¹-Q16-(CH₂)_z-

wherein R¹ is as defined above, Q16 represents a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl, and z represents an integer of 0 to 4,

Z represents

a hydrogen atom,

a halogen atom,

a three- to seven-membered saturated or unsaturated monocyclic carbocyclic or heterocyclic group,

a nine- to twelve-membered bicyclic saturated or unsaturated carbocyclic or heterocyclic group, or

a thirteen- to fifteen-membered tricyclic saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic and heterocyclic groups are optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a

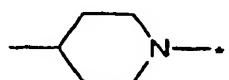
halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy of which the phenyl portion is optionally substituted by a halogen atom,

5 provided that

when X represents group (i) wherein Q1 represents a bond and Z represents 2-ethoxycarbonyl-phenyl, 2-methoxy-phenyl, 2-nitro-phenyl, or 4-nitro-phenyl, Het does not represent 4-pyridyl, and

when X represents group (iv) wherein R¹ represents a hydrogen atom, Q6 represents formula

10



15

wherein the bond with * represents a bond to Q7, and Q7 represents -CH₂-CH₂-, and Z represents an unsubstituted phenyl, Het does not represent 1-piperidinyl, 4-morpholinyl, 3-pyridinyl, 4-pyridinyl, 2-chloro-3-pyridinyl, 2-chloro-5-pyridinyl, 5-indolyl, 5-indazolyl, 3-quinolinyl, or 2,1,3-benzothiadiazol-4-yl.

20 2. The compound according to claim 1, wherein the monocyclic heterocyclic group represented by Het represents a group represented by formula (IIa), (IIb), or (IIc):

25



30 wherein A1 represents a five- to seven-membered monocyclic saturated or unsaturated heterocyclic group having at least one nitrogen atom.

35

3. The compound according to claim 1 or 2, wherein the monocyclic heterocyclic group represented by Het is pyridyl, pyrimidyl, isoxazoyl, isothiazoyl, 1,2,3-oxadiazoyl, furazanyl, 1,2,3-triazoyl, 1,2,4-triazoyl, pyridazyl, pyrrolinyl, or triazinyl.

40

4. The compound according to claim 1, wherein the bicyclic heterocyclic group represented by Het represents formula (IIIa), (IIIb), (IIIc), (IIId), (IIIE), (IIIf), (II Ig), (II Ih), (II Ii), or (II Ij):

45



50



55

5



10

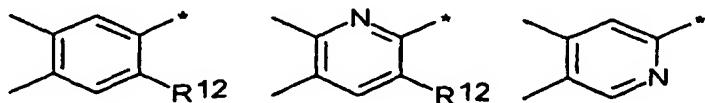


15

wherein A2 represents phenyl optionally substituted by a halogen atom, or an unsaturated six-membered heterocyclic ring which is optionally substituted by a halogen atom and contains one or two nitrogen atoms; R¹¹ represents a hydrogen atom or C₁₋₄ alkylcarbonyl; and E represents -NH-, -O-, or -S-.

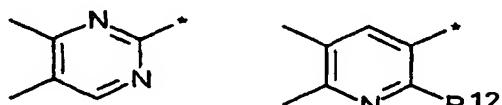
- 20 5. The compound according to claim 4, wherein the A2 portion is selected from the group consisting of the following groups:

25



30

35



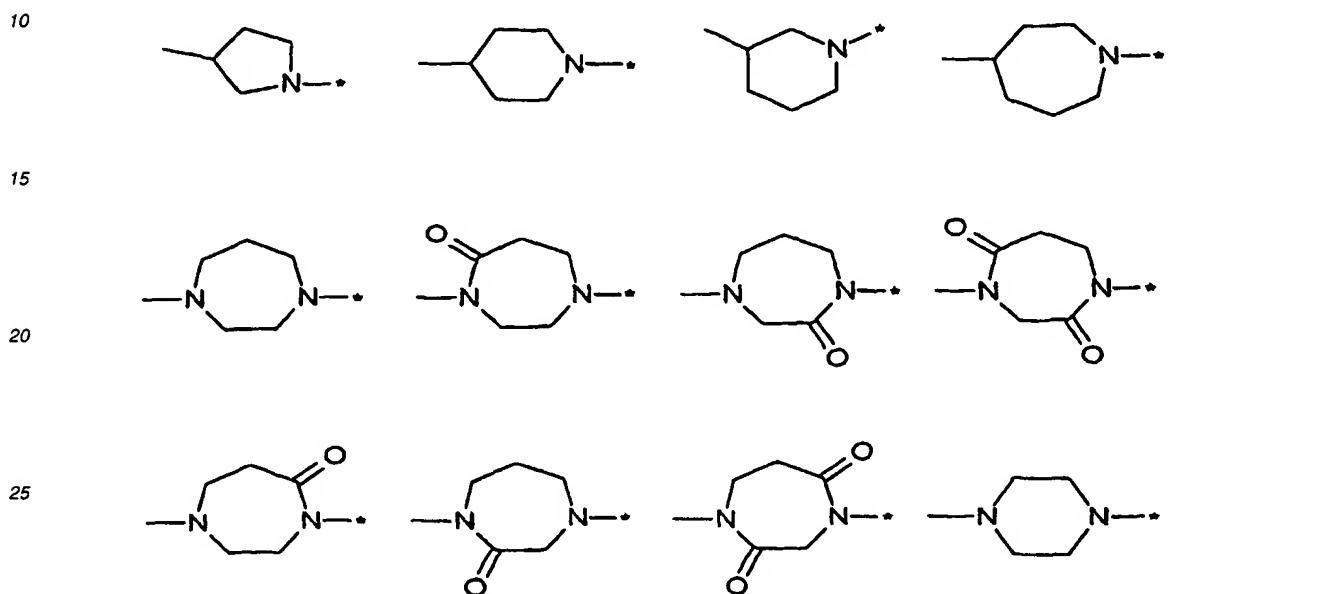
wherein R¹² represents a hydrogen atom or a halogen atom; and a bond with * represents a bond to group X with the remaining two bonds each representing a bond to the heterocyclic group.

- 40 6. The compound according to claim 1 or 4, wherein the bicyclic heterocyclic group represented by Het is 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, quinolinyl, isoquinolinyl, sinolinyl, quinazolinyl, phthalazinyl, pteredinyl, naphthyridinyl, benzimidazolinyl, benzothiazolinyl, or benzoxazolinyl.
- 45 7. The compound according to claim 1, wherein X represents group (i) wherein Q1 represents a bond, alkylene having 1 to 3 carbon atoms, or alkenylene having 2 or 3 carbon atoms and the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl.
- 50 8. The compound according to claim 1, wherein X represents group (ii) wherein Q2 represents a bond, alkylene having 1 to 3 carbon atoms, or alkenylene having 2 or 3 carbon atoms and the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl.
- 55 9. The compound according to claim 1, wherein X represents group (iii) wherein Q3 represents alkylene having 1 or 2 carbon atoms or alkenylene having 2 carbon atoms; Q4 represents -O-, -NH-, or -S(=O)m- wherein m is an integer of 0 to 2; and Q5 represents a bond, alkylene having 1 or 2 carbon atoms, or alkenylene having 2 carbon atoms and the alkylene and alkenylene represented by Q5 represent C₁₋₄ alkyl or optionally substituted phenyl.

10. The compound according to claim 1, wherein X represents group (iv) wherein R¹ represents a hydrogen atom or C₁₋₄ alkylcarbonyl; Q6 represents a bond, a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents a bond, -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2-, wherein n1 is an integer of 0 or 1, n2 is 0, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, -(CH₂)p-NR³-, wherein p is an integer of 0 or 1, R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, or -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2-wherein q1 is 0 or 1, q2 is 0, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl or optionally substituted phenyl.
11. The compound according to claim 1, wherein X represents group (iv) wherein R¹ represents a hydrogen atom or C₁₋₄ alkylcarbonyl; Q6 represents a bond, a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents a bond, -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2-, wherein n1 and n2 are each an integer of 0 to 3, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, optionally substituted C₁₋₆ alkyl, carboxyl, C₁₋₄ alkoxy carbonyl, cyano, -(C=O)-N(-R^{2c})(-R^{2d}), wherein R^{2c} and R^{2d}, which may be the same or different, represent a hydrogen atom, optionally substituted C₁₋₄ alkyl, optionally substituted C₁₋₄ alkoxy, cyclopropyl, or optionally substituted benzyl, or optionally substituted phenyl, -(CH₂)p-NR³-, wherein p is an integer of 0 or 1, R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2-, wherein q1 and q2 are each an integer of 0 to 2, R^{4a} represents a hydrogen atom, R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, -(C=O)-O-CR^{4a}R^{4b}-CH₂-, wherein R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, optionally substituted C₁₋₆ alkyl, or optionally substituted phenyl, -NH-(CH₂)i-NH-, wherein i is an integer of 1 to 4, or -S(=O)j- wherein j is 0, 1, or 2.
12. The compound according to claim 10, wherein, in group (iv), R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom; and Q7 represents -(CH₂)p-NR³-, wherein p is an integer of 0 or 1 and R³ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, or -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2-, wherein q1 is 0 or 1, q2 is 0, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.
13. The compound according to claim 10, wherein, in group (iv), R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated heterocyclic group which is optionally substituted by an oxygen atom and contains one nitrogen atom; and Q7 represents -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 is an integer of 0 or 1, n2 is 0, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.
14. The compound according to claim 11, wherein, in group (iv), R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 and n2, which may be the same or different, are each an integer of 0 to 3, R^{2a} represents a hydrogen atom, and R^{2b} represents a hydrogen atom or optionally substituted C₁₋₄ alkyl.
15. The compound according to claim 11, wherein, in group (iv), R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 and n2 are each 0, R^{2a} represents a hydrogen atom, and R^{2b} represents optionally substituted C₁₋₆ alkyl, carboxyl, C₁₋₄ alkoxy carbonyl, cyano, -(C=O)-N(-R^{2c})(-R^{2d}), wherein R^{2c} and R^{2d} are as defined in claim 1, or optionally substituted phenyl.
16. The compound according to claim 11, wherein, in group (iv), R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2- wherein n1 is an integer of 0 to 3, n2 is 0, and R^{2a} and R^{2b} represent a halogen atom.
17. The compound according to claim 11, wherein, in group (iv), R¹ represents a hydrogen atom; Q6 represents a five- to seven-membered saturated carbocyclic group or a five- to seven-membered saturated heterocyclic group con-

taining one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom; and Q7 represents -NH-(CH₂)q1-CR^{4a}R^{4b}-(CH₂)q2- wherein q1 and q2 are each an integer of 0 to 2, R^{4a} represents a hydrogen atom, and R^{4b} represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.

- 5 18. The compound according to any one of claims 1 and 10 to 17, wherein, in group (iv), Q6 represents any one of the following groups:



30 wherein the bond with * represents a bond to Q7 and the bond without * represents a bond to group -N(-R1)-.

- 35 19. The compound according to claim 10, wherein, in group (iv), R¹ represents a hydrogen atom, Q6 represents a bond, and Q7 represents a bond.
- 40 20. The compound according to claim 1, wherein X represents group (v) wherein Q8 represents alkylene having 1 to 3 carbon atoms or alkenylene having 2 or 3 carbon atoms; Q9 represents -O-, -NH-, or -S(=O)r- wherein r is an integer of 0 to 2; and Q10 represents a bond, alkylene having 1 or 2 carbon atoms or alkenylene having 2 carbon atoms and the alkylene and alkenylene represented by Q10 are optionally substituted by C₁₋₄ alkyl or optionally substituted phenyl.
- 45 21. The compound according to claim 1, wherein X represents group (vi) wherein Q11 represents a bond, a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom, or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom; and Q12 represents a bond, -(CH₂)s-CHR⁵-, wherein s is an integer of 0 or 1 and R⁵ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, -(CH₂)t-NR⁶-, wherein t is an integer of 0 or 1 and R⁶ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, or -NH-(CH₂)u-CHR⁷- wherein u is an integer of 0 or 1 and R⁷ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.
- 50 22. The compound according to claim 1, wherein X represents group (vii) wherein Q13 represents a bond, a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom, or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom; and Q14 represents a bond, -(CH₂)v-CHR⁸-, wherein v is an integer of 0 or 1 and R⁸ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, -(CH₂)w-NR⁹-, wherein w is an integer of 0 or 1 and R⁹ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl, or -NH-(CH₂)x-CHR¹⁰- wherein x is an integer of 0 or 1 and R¹⁰ represents a hydrogen atom, C₁₋₄ alkyl, or optionally substituted phenyl.
- 55 23. The compound according to claim 1, wherein X represents group (viii) wherein Q15 represents a five- to seven-

membered saturated heterocyclic group which is optionally substituted by an oxygen atom and contains two nitrogen atoms; and y is 1 or 2.

- 5 24. The compound according to claim 1, wherein X represents group (ix) wherein Q16 represents a five- to seven-membered saturated carbocyclic group optionally substituted by an oxygen atom, or a five- to seven-membered saturated heterocyclic group containing one nitrogen atom; and z is 1 or 2.
- 10 25. The compound according to claim 1, wherein Z represents
 a hydrogen atom,
 a halogen atom,
 a three- to seven-membered saturated or unsaturated carbocyclic group,
 a five- to seven-membered saturated or unsaturated heterocyclic group containing one nitrogen atom and/or one oxygen atom,
 a nine- or ten-membered unsaturated bicyclic carbocyclic group,
 a nine- or ten-membered unsaturated bicyclic heterocyclic group containing one nitrogen atom and/or one or two oxygen atoms, or
 a thirteen- to fifteen-membered unsaturated tricyclic carbocyclic group or heterocyclic group.
- 15 26. The compound according to claim 25, wherein Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl which is optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy of which the phenyl portion is optionally substituted by a halogen atom.
- 20 27. The compound according to claim 1, wherein
 Het represents a monocyclic heterocyclic group represented by formula (IIa), (IIb), or (IIc) as defined in claim 2, or represents a bicyclic heterocyclic group represented by formula (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), (IIIh), (IIIi), or (IIIj) as defined in claim 4 or 5,
 X represents group (i) as defined in claim 7, group (ii) as defined in claim 8, group (iii) as defined in claim 9, group (iv) as defined in any one of claims 10 to 19, group (v) as defined in claim 20, group (vi) as defined in claim 21, group (vii) as defined in claim 22, group (viii) as defined in claim 23, or group (ix) as defined in claim 24, and
 Z represents a hydrogen atom, a halogen atom, phenyl, cyclopropyl, cyclohexyl, furanyl, pyridyl, piperidyl, naphthyl, naphthalenyl, indenyl, indolyl, imidazolyl, thienyl, 1,3-benzodioxole, fluorenyl, or carbazolyl and these groups are optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl which is optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxycarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy of which the phenyl portion is optionally substituted by a halogen atom.
- 25 28. The compound according to claim 27, wherein Het represents 4-pyridyl, 1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1H-5-indazolyl, 6-chloro-1,3-dioxy-2,3-dihydro-1H-5-isoindolyl, 1-acetyl-1H-5-indazolyl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 1H-5-benzotriazolyl, or 5-isoquinolyl.
- 30 29. The compound according to claim 1, selected from the group consisting the following compounds:
 (20) N-[1-(4-bromophenyl)ethyl]-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea;
 (21) N-(1-benzyl-3-piperidyl)-N-(1H-5-indazolyl)-amine;
 (22) N-[1-(4-bromobenzyl)-4-piperidyl]-N-(1H-5-imidazolyl)amine;
 (80) N-(2,6-dichlorobenzyl)-N'-(4-pyridyl)urea;
 (83) N-(2-chloro-6-fluorobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-6-isoindolyl)urea;
 (90) N-(2,6-difluorobenzyl)-N'-(1,3-dioxo-2,3-dihydro-1H-5-isoindolyl)urea;
 (95) N-(2,6-difluorobenzyl)-N'-(1H-5-indazolyl)-urea;
 (102) N-(2-chloro-6-fluorobenzyl)-N'-(1H-5-indazolyl)urea;
 (126) N-(1-benzyl-4-piperidyl)-N-(1H-5-indazolyl)-amine;
 (127) N-(1-benzyl-4-piperidyl)-N-(1H-5-indazolyl)-amine hydrochloride;

- (128) N-(1H-5-indazolyl)-N-(4-piperidyl)amine;
 (146) N-(1-benzyl tetrahydro-1H-pyrrolyl)-N-(1H-5-indazolyl)amine;
 (164) N-[1-(4-fluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine;
 (221) methyl 2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetate;
 (227) N1-(2-fluoroethyl)-2-[3-(1H-5-indazolylamino)piperidino]-2-phenylacetamide;
 (240) N-(1H-5-indazolyl)-N-[1-(2-methyl-1-phenylpropyl)-3-piperidyl]amine;
 1.1. (243) N1-(1H-5-indazolyl)-N4-propyl-1,4-cyclohexanediamine;
 (246) N1-(2-fluoroethyl)-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine;
 (247) N1-cyclopropyl-N4-(1H-5-indazolyl)-1,4-cyclohexanediamine;
 (248) N1-(1H-5-indazolyl)-1,4-cyclohexanediamine;
 (259) N1-(1H-5-indazolyl)-N4-phenylethyl-1,4-cyclohexanediamine;
 (260) N1-(5-isoquinolyl)-N4-propyl-1,4-cyclohexanediamine;
 (261) N1-(2-fluoroethyl)-N4-(5-isoquinolyl)-1,4-cyclohexanediamine;
 (262) N1-cyclopropyl-N4-(5-isoquinolyl)-1,4-cyclohexanediamine;
 (273) N-(5-isoquinolyl)-N-[1-(4,4,4-trifluorobutyl)-3-piperidyl]amine;
 (281) N-(1H-5-indazolyl)-N-[1-(2-methylpentyl)-3-piperidyl]amine;
 (282) N-(1H-5-indazolyl)-N-[1-(2,4,6-trifluorobenzyl)-3-piperidyl]amine;
 (286) N-(1H-5-indazolyl)-N-(1-propyl-4-piperidyl)-amine;
 (287) N-[1-(cyclopropylmethyl)-4-piperidyl]-N-(1H-5-indazolyl)amine;
 (289) N-[1-(3-fluoropropyl)-4-piperidyl]-N-(1H-5-indazolyl)amine;
 (290) N-(1H-5-indazolyl)-N-[1-(3,3,3-trifluoropropyl)-4-piperidyl]amine;
 (293) N-[1-(2-chloro-4-fluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine;
 (294) methyl 2-(3,4-difluoropentyl)-2-[3-(1H-5-indazolylamino)piperidino]acetate;
 (298) N-(1H-5-indazolyl)-N-{1-[4-(trifluoromethyl)-benzyl]-3-piperidyl}amine;
 (300) N-[1-(3,4-difluorobenzyl)-3-piperidyl]-N-(1H-5-indazolyl)amine;
 (318) N-(5-isoquinolyl)-N-(1-propyl-4-piperidyl)-amine;
 (320) N-[1-(2-ethylbutyl)-4-piperidyl]-N-(5-isoquinolyl)amine; and
 (322) N-[1-(3-fluoropropyl)-4-piperidyl]-N-(5-isoquinolyl)amine.

30 30. A pharmaceutical composition comprising the compound according to any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof.

31. A pharmaceutical composition comprising a compound represented by formula (Ia) or a pharmaceutically acceptable salt or solvate thereof, for use in the therapy of diseases mediated by Rho kinase:

35 Het-X-Z (Ia)

40 wherein

Het represents a five- to seven-membered monocyclic saturated or unsaturated heterocyclic group containing at least one nitrogen atom, or a nine- to twelve-membered bicyclic saturated or unsaturated heterocyclic group containing at least one nitrogen atom and the carbocyclic and heterocyclic groups are optionally substituted by a halogen atom, an oxygen atom, hydroxyl, or C₁₋₄ alkylcarbonyl,

45 X represents a group selected from the group consisting of groups (i) to (ix):

(i) -NH-C(=O)-NH-Q1-

50 wherein

Q1 represents

a bond,

alkylene having 1 to 4 carbon atoms, or

alkenylene having 2 to 4 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by

55 C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

(ii) -NH-C(=O)-Q2-

wherein

5 Q2 represents
 a bond,
 alkylene having 1 to 5 carbon atoms, or
 alkenylene having 2 to 5 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by
 10 C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally
 substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom;
 C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of
 15 which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion
 is optionally substituted by a halogen atom; or benzyloxy,

(iii) -NH-C(=O)-Q3-Q4-Q5-

wherein

20 Q3 represents
 alkylene having 1 to 4 carbon atoms or
 alkenylene having 2 to 4 carbon atoms,
 Q4 represents -O-, -NH-, or -S(=O)m- wherein m is an integer of 0 to 2,
 Q5 represents
 a bond,
 25 alkylene having 1 to 3 carbon atoms, or
 alkenylene having 2 or 3 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by
 C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally
 substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom;
 30 C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of
 which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion
 is optionally substituted by a halogen atom; or benzyloxy,

(iv) -N(-R¹)-Q6-Q7-

wherein

35 R¹ represents a hydrogen atom or C₁₋₄ alkyl carbonyl,
 Q6 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic
 40 group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄
 alkyl,
 Q7 represents
 a bond,

45 -(CH₂)n1-CR^{2a}R^{2b}-(CH₂)n2-

wherein

n1 and n2 are each an integer of 0 to 3,
 when n2 is 2 or 3, -CH₂-CH₂- in -(CH₂)n2- may represent -CH=CH- or -C≡C-,
 50 R^{2a} and R^{2b}, which may be the same or different, represent
 a hydrogen atom,
 a halogen atom,
 C₁₋₆ alkyl optionally substituted by hydroxyl,
 carboxyl,
 55 C₁₋₄ alkoxy carbonyl,
 cyano,
 -(C=O)-N(-R^{2c})(-R^{2d}) wherein R^{2c} and R^{2d}, which may be the same or different, represent a hydrogen atom;
 C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy optionally substituted by a halogen atom; cyclo-

propyl; or benzyl of which the phenyl portion is optionally substituted by one or two C₁₋₄ alkoxy, or phenyl optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

- $(\text{CH}_2)_p\text{NR}^3$, wherein p is an integer of 0 to 2, R³ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

-NH-(CH₂)q₁-CR^{4a}R^{4b}-(CH₂)q₂- wherein q₁ and q₂ are each an integer of 0 to 2 and R^{4a} and R^{4b} each independently represent a hydrogen atom, C₁₋₄ alkyl or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

-(C=O)-O-CR^{4a}R^{4b}.CH₂, wherein R^{4a} and R^{4b} are as defined above,

-NH-(CH₂)i-NH- wherein i is an integer of 1 to 4, or

-S(=O)_j- wherein j is 0, 1, or 2,

(v) -NH-Q8-Q9-Q10-

wherein

Q8 represents

alkylene having 1 to 5 carbon atoms or
alkenylene having 2 to 5 carbon atoms,

Q9 represents -O-, -NH-, or -S(=O)r- wherein r is an integer of 0 to 2,

Q10 represents

a bond,

alkylene having 1 to 3 carbon atoms, or

alkenylene having 2 or 3 carbon atoms, wherein the alkylene and alkenylene are optionally substituted by C₁₋₄ alkyl or phenyl optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

wherein

Q11 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

Q12 represents

a bond,

-(CH₂)_s-CHR⁵- wherein s is an integer of 0 to 2 and R⁵ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

-(CH₂)_t-NR⁶- wherein t is an integer of 0 to 2 and R⁶ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of

(vi)-O-Q11-Q12-

which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy, or

-NH-(CH₂)^u-CHR⁷- wherein u is an integer of 0 or 1 and R⁷ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl

which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

10

(vii)-Q13-Q14-

wherein

Q13 represents a bond or a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl,

Q14 represents

a bond,

- (CH₂)^v-CHR⁸- wherein v represents an integer of 0 to 2 and R⁸ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

- (CH₂)^w-NR⁹- wherein w represents an integer of 0 to 2 and R⁹ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy, or

-NH-(CH₂)^x-CHR¹⁰- wherein x is an integer of 0 or 1 and R¹⁰ represents a hydrogen atom, C₁₋₄ alkyl, or phenyl which is optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkylcarbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy,

40

(viii) -C(=O)-Q15-(CH₂)^y-

wherein Q15 represents a five- to seven-membered saturated or unsaturated heterocyclic group and this heterocyclic group is optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl and y is an integer of 0 to 4, and

45

(ix) -C(=O)-NR¹-Q16-(CH₂)^z-

wherein R¹ is as defined above, Q16 represents a five- to seven-membered saturated or unsaturated carbocyclic or heterocyclic group and the carbocyclic and heterocyclic groups are optionally substituted by an oxygen atom, hydroxyl, or C₁₋₄ alkyl, and z represents an integer of 0 to 4,

Z represents

a hydrogen atom,

a halogen atom,

a three- to seven-membered saturated or unsaturated monocyclic carbocyclic or heterocyclic group,

a nine- to twelve-membered bicyclic saturated or unsaturated carbocyclic or heterocyclic group, or

a thirteen- to fifteen-membered tricyclic saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic and heterocyclic groups are optionally substituted by a halogen atom; hydroxyl; nitro; amino; C₁₋₄ alkyl optionally substituted by a halogen atom; C₁₋₄ alkoxy of which the alkyl portion is optionally substituted by a

50

55

halogen atom; C₁₋₄ alkoxy carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyl of which the alkyl portion is optionally substituted by a halogen atom; C₁₋₄ alkyl carbonyloxy of which the alkyl portion is optionally substituted by a halogen atom; or benzyloxy of which the phenyl portion is optionally substituted by a halogen atom.

- 5
32. The pharmaceutical composition according to claim 31, wherein the disease mediated by Rho kinase is selected from the group consisting of hypertension, asthma including bronchial asthma, angina pectoris, cerebrovascular spasm, peripheral circulatory disorder, threatened premature birth, glaucoma, constriction of visual field, pollakiuria, cancer, invasion/metastasis of cancer, arteriosclerosis, retinopathy, immune response, inflammation, autoimmune diseases, cerebral dysfunction, osteoporosis, microbism, chronic renal failure, chronic nephritis, diabetic nephropathy, IgA nephropathia, thrombosis-related diseases, rheumatism, impotence, and fibrosis.
- 10
33. A method for treating a disease mediated by Rho kinase, comprising the step of administering the compound represented by formula (Ia) as defined in claim 31 or a pharmaceutically acceptable salt or solvate thereof together with a pharmaceutically acceptable carrier, to a mammal.
- 15
34. Use of the compound represented by formula (Ia) as defined in claim 31 or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of a disease mediated by Rho kinase.

20

25

30

35

40

45

50

55

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/00721

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl⁷ C07D209/48, 213/75, 217/02, 231/56, 401/12, 401/14, 403/12, 405/12, 405/14, 487/04, A61K31/4035, 404, 416, 4409, 4439, 454, 4545, 472, 4725, 496, 519, A61P43/00, 9/10, 9/12, 11/06, 13/02, 15/06, 15/10, 27/06, C07C275/42
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl⁷ C07D209/48, 213/75, 217/02, 231/56, 401/12, 401/14, 403/12, 405/12, 405/14, 487/04, A61K31/4035, 404, 416, 4409, 4439, 454, 4545, 472, 4725, 496, 519, A61P43/00, 9/10, 9/12, 11/06, 13/02, 15/06, 15/10, 27/06, C07C275/42

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, 98/06433, A1 (YOSHITOMI PHARMACEUTICAL INDUSTRIES LTD.), 19 February, 1998 (19.02.98), Full text, & AU, 9737851, A1 & BR, 9711154, A & CN, 1233188, A & EP, 956865, A1 & NO, 9900622, A	1-32, 34
X	WO, 92/12961, A1 (RHONE-POULENC RORER LTD.), 06 August, 1992 (06.08.92), example, & US, 5935978, A & ZA, 9200547, A & AU, 9211881, A & EP, 569414, A1 & JP, 6-504782, A & NO, 9302701, A & ZA, 9305448, A & FI, 9500375, A & US, 5679696, A & US, 5698711, A & US, 5840724, A & US, 6096768, A	1-3, 8, 25-28, 30-32, 34
X	WO, 95/07075, A1 (SYNAPTIC PHARMACEUTICAL CORP.), 16 March, 1995 (16.03.95), example, (RN=5221-44-3) & US, 5508306, A & US, 5403847, A	1-3, 8, 25-28, 30-32, 34

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier document but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search 19 April, 2001 (19.04.01)	Date of mailing of the international search report 01 May, 2001 (01.05.01)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/00721

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& CA, 2148839, A & ZA, 9308510, A & AU, 9476848, A & US, 5780485, A	
EX	WO, 01/015677, A1 (ALCON LABORATORIES. INC.), 08 March, 2001 (08.03.01), example, (RN=162401-32-3) (Family: none)	1-3, 8, 25-28, 30-32, 34
X	US, 5955496, A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 21 September, 1999 (21.09.99), example, (RN=148806-83-1) & US, 6150415, A	1-3, 7, 25-28, 30-32, 34
PX	WO, 00/048998, A1 (DARWIN DISCOVERY LIMITED), 24 August, 2000 (24.08.00), example, (RN=208261-57-8, etc.) (Family: none)	1-3, 8, 25-28, 30-32, 34
PX	WO, 00/026208, A1 (DARWIN DISCOVERY LIMITED), 11 May, 2000 (11.05.00), example, (RN=266995-21-5, etc.) & BR, 9906719, A & EP, 1045845, A1 & NO, 2000003439, A	1-3, 8, 25-28, 30-32, 34
X	WO, 99/64423, A1 (DARWIN DISCOVERY LIMITED), 16 December, 1999 (16.12.99), example, (RN=252029-12-2, etc.) & AU, 9942776, A & EP, 1086106, A1 & US, 6169090, A	1-3, 8, 25-28, 30-32, 34
X	WO, 99/38867, A1 (SUNTORY LIMITED), 05 August, 1999 (05.08.99), example, (RN=233763-84-3, etc.) & AU, 9921856, A & EP, 978516, A1	1-6, 8, 24-28, 30-32, 34
X	WO, 99/37640, A1 (KYOWA HAKKO KOGYO CO., LTD.), 29 July, 1999 (29.07.99), example, (RN=185400-39-9) & AU, 9919835, A	1-3, 8, 25-28, 30-32, 34
X	JP, 11-139969, A (TANABE SEIYAKU CO., LTD.), 25 May, 1999 (25.05.99), example, (RN=195312-57-3) (Family: none)	1-3, 7, 24-28, 30-32, 34
X	WO, 99/21836, A1 (SMITHKLINE BEECHAM PLC), 06 May, 1999 (06.05.99), example, (RN=223698-52-0, etc.) & EP, 1025087, A1	1, 4, 6, 8, 25-28, 30-32, 34
X	WO, 99/16768, A1 (KYOWA HAKKO KOGYO CO., LTD.), 08 April, 1999 (08.04.99), example, (RN=22297-34-9) & AU, 9892811, A & EP, 1029860, A1	1-3, 8, 25-28, 30-32, 34
X	WO, 99/00357, A1 (VERTEX PHARMACEUTICALS), 07 January, 1999 (07.01.99), example, (RN=218135-64-9, etc.) & US, 6093742, A & AU, 9883776, A & EP, 993441, A1	1-7, 24-28, 30-32, 34

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/00721

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, 98/22455, A1 (KYOWA HAKKO KOGYO CO., LTD.), 28 May, 1998 (28.05.98), example, (RN=208043-33-8, etc.) & AU, 9749676, A & EP, 934613, A1	1-3, 8, 25-28, 30-32, 34
X	JP, 10-147585, A (KYOWA HAKKO KOGYO CO., LTD.), 02 June, 1998 (02.06.98), example, (RN=185405-62-3, etc.) (Family: none)	1-3, 8, 25-28, 30-32, 34
X	WO, 98/09961, A1 (PFIZER INC.), 12 March, 1998 (12.03.98), example, (RN=204256-11-1, etc.) & AU, 9737813, A & EP, 931075, A1 & BR, 9712005, A & CN, 1234031, A & JP, 2000-502724, A & NO, 9901048, A	1-6, 8, 24-28, 30-32, 34
X	WO, 97/49399, A1 (SMITHKLINE BEECHAM CORP.), 31 December, 1997 (31.12.97), example, (RN=201532-51-6) & EP, 907362, A1	1-3, 7, 25-28, 30-32, 34
X	WO, 97/48697, A1 (REGAN JOHN ROBINSON), 24 December, 1997 (24.12.97), example, (RN=201285-12-3, 201285-59-8, etc.) & CA, 2258728, A & AU, 9731026, A & ZA, 9705446, A & EP, 934307, A1 & JP, 2000-509719, A	1-3, 8, 24-28, 30-32, 34
X	WO, 97/44337, A1 (CHIROSCIENCE LIMITED), 27 November, 1997 (27.11.97), example, (RN=192380-73-7, etc.) & WO, 97/20833, A1 & AU, 9729060, A & EP, 901482, A1 & BR, 9709113, A & JP, 2000-510848, A & NO, 9805375, A	1-4, 8, 25-28, 30-32, 34
X	WO, 97/44036, A1 (CHIROSCIENCE LIMITED), 27 November, 1997 (27.11.97), example, (RN=199871-47-1, 199871-78-8, etc.) & AU, 9729058, A & US, 5804588, A & CN, 1219131, A & BR, 9709015, A & EP, 952832, A1 & JP, 2000-510865, A & NO, 9805376, A	1-4, 6, 8, 24-28, 30-32, 34
X	WO, 97/20833, A1 (CHIROSCIENCE LIMITED), 12 June, 1997 (12.06.97), example, (RN=192380-72-6, etc.) & CA, 2238376, A & AU, 9710386, A & US, 5773467, A & EP, 873331, A1 & CN, 1208411, A & BR, 9611897, A & JP, 2000-501411, A & EP, 901482, A1 & WO, 97/44337, A1 & AU, 9729060, A & CN, 1219171, A & US, 5925636, A & BR, 9709113, A & US, 5972936, A & JP, 2000-510848, A & NO, 9802570, A & NO, 9805375, A	1-3, 8, 25-28, 30-32, 34
X	WO, 97/03967, A1 (RHONE-POULENC RORER LIMITED), 06 February, 1997 (06.02.97), example, (RN=144036-24-8) & AU, 9665268, A	1-3, 8, 25-28, 30-32, 34

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/00721

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, 96/04266, A2 (ASTA MEDICA AG), 15 February, 1996 (15.02.96), example, (RN=176204-46-9) & DE, 19511916, A & CA, 2195850, A & AU, 9531626, A & EP, 775131, A2 & JP, 10-503501, A & ZA, 9506382, A & IL, 114795, A & NO, 9700412, A & FI, 9701334, A & US, 5965582, A	1-3, 8, 25-28, 30-32, 34
X	WO, 95/20578, A1 (RHONE-POULENC RORER LTD.), 03 August, 1995 (03.08.95), example, (RN=144035-93-8, etc.) & AU, 9514631, A & ZA, 9500639, A & EP, 741707, A1 & JP, 9-509654, A	1-3, 8, 25-28, 30-32, 34
X	WO, 95/04045, A1 (RHONE-POULENC RORER LTD.), 09 February, 1995 (09.02.95), example, (RN=166741-50-0, etc.) & CA, 2160928, A & AU, 9472670, A & ZA, 9405609, A & EP, 711282, A1 & JP, 9-501155, A	1-3, 8, 25-28, 30-32, 34
X	WO, 91/17748, A1 (HOESCH A.-G.), 28 November, 1991 (28.11.91), example, (RN=139442-42-5) & CA, 2083179, A & AU, 9065468, A & EP, 527736, A1 & BR, 9008022, A & JP, 5-506425, A & HU, 64314, A & JP, 11-322700, A & JP, 11-343285, A & CN, 1056684, A & IL, 98163, A & ZA, 9103762, A & US, 5494911, A & NO, 9204433, A & AU, 9457992, A & FI, 9501697, A & US, 5532259, A	1, 4-6, 8, 25-28, 30-32, 34
X	WO, 88/08424, A1 (UPJOHN CO.), 03 November, 1988 (03.11.88), example, (RN=122003-40-1) & CA, 1338012, A & EP, 293078, A1 & AU, 8817098, A & EP, 358676, A1 & JP, 2-503198, A & EP, 487510, A1 & US, 5120843, A & DK, 8905335, A	1-3, 8, 25-28, 30-32, 34
X	EP, 277791, A1 (FARMITALIA CARLO ERBA S.P.A.), 10 August, 1988 (10.08.88), example, (RN=117484-18-1, etc.) & US, 4826837, A & IL, 85221, A & FI, 8800376, A & FI, 8800376, A & AU, 8810908, A & DK, 8800484, A & ZA, 8800686, A & SU, 1563592, A & HU, 56551, A & CA, 1309407, A & JP, 63-225363, A	1-3, 8, 24-28, 30-32, 34
X	EP, 168005, A2 (FUJISAWA PHARMACEUTICAL COL., LTD.), 15 January, 1986 (15.01.86), example, (RN=102671-35-2, etc.) & ZA, 8503658, A & CA, 1270828, A & ZA, 8504638, A & US, 4694004, A & CA, 1256434, A & DK, 8503000, A & ES, 544963, A & JP, 61-44864, A & ES, 552537, A & ES, 552536, A	1-3, 7, 25-28, 30-32, 34

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/00721

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB, 2009155, A (LOEVENS KEMISKE FABRIK PRODUKTION SAKTIESELSKAB), 13 June, 1979 (13.06.79), example, (RN=71070-96-7, etc.) & DE, 2847792, A & US, 4293549, A & AT, 7807732, A & CA, 1120929, A & FI, 7803327, A & ZA, 7806175, A & CH, 645354, A & SU, 828967, A & BE, 871807, A & DK, 7804933, A & SE, 7811457, A & NL, 7811035, A & AU, 7841376, A & FR, 2407930, A & JP, 63-48873, B & ES, 474900, A	1, 6, 7, 25-28, 30-32, 34
X	US, 4022900, A (MARION LABORATORIES), 10 May, 1977 (10.05.77), example, (RN=37481-27-9, etc.) & US, 3674791, A & BE, 763149, A	1, 4-6, 8, 25-28, 30-32, 34
X	WO, 96/37473, A1 (HOECHST SCHERING AGREVO GMBH), 28 November, 1996 (28.11.96), example, (RN=168086-47-3, etc.) & AU, 9526165, A	1, 4, 6, 10-19
X	WO, 96/24586, A1 (BOEHRINGER MANNHEIM GMBH), 15 August, 1996 (15.08.96), example, (RN=181258-50-4) & DE, 19504367, A & CA, 2212336, A & AU, 9647886, A & EP, 808306, A1 & JP, 11-504618, A & US, 5786731, A	1-3, 10-19
X	EP, 656353, A1 (F.HOFFMANN-LA ROCHE AG), 07 June, 1995 (07.06.95), example, (RN=169815-43-4, etc.) & CA, 2133620, A & ZA, 9408305, A & AU, 9477419, A & JP, 7-188174, A & US, 5596002, A & CN, 1106389, A & BR, 9501222, A & CN, 1245168, A	1-4, 6, 10-19, 25-27, 30
X	WO, 95/07891, A1 (HOECHST SCHERING AGREVO GMBH), 23 March, 1995 (23.03.95), example, (RN=164720-77-8, etc.) & DE, 4331179, A & AU, 9476152, A & EP, 719256, A1 & CN, 1130901, A & BR, 9407541, A & JP, 9-502446, A & US, 5723450, A & ZA, 9407040, A	1-3, 10-19, 25-28, 30
X	WO, 94/21613, A1 (HOECHST SCHERING AGREVO GMBH), 29 September, 1994 (29.09.94), example, (RN=159228-43-0) & DE, 4308014, A & CA, 2158160, A & AU, 9462583, A & EP, 701552, A1 & CN, 1119436, A & JP, 8-507539, A & ZA, 9401715, A & US, 5821244, A	1, 4, 6, 10-19, 25-27
X	BARGLEY J.R. et al., "New 4-(heteroanilido)piperidines, structurally related to the pure opipodagonist fentanyl, with agonist and/or antagonist properties", J. Med. Chem., (1989), 32(3), p.663-71	1-3, 10-19, 25-27

INTERNATIONAL SEARCH REPORT		International application No. PCT/JP01/00721
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SINGH T. et al., "Antimalarials. 7-chloro-4-(substituted amino)quinolines", J. Med. Chem., (1971), 14(4), pp.283-6	1, 4, 6, 10-19, 25-27, 30

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/00721

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 33
because they relate to subject matter not required to be searched by this Authority, namely:
The invention as set forth in claim 33 pertains to methods for treatment of the human body by therapy.
2. Claims Nos.: 1-32,34
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See extra sheet.
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Since Het, X and Z are each variable in the compounds relating to the inventions as set forth in claims 1 to 32 and 34, these compounds have no chemical structure in common but involve, in addition to those as cited in the following column C, an extremely large number of publicly known compounds such as pyrrole and pyridine. Therefore, these compounds have no important chemical structure in common. Such being the case, the inventions as set forth in the above claims are not considered as relating to a single invention or a group of inventions so linked as to form a single general inventive concept.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/00721

Continuation of Box No.I.2 of Continuation of first sheet (1)

Since Het, X and Z are each variable in the compounds relating to the inventions as set forth in claims 1 to 32 and 34, these compounds have no chemical structure in common but involve, in addition to those as cited in the above column C, an extremely large number of publicly known compounds such as pyrrole and pyridine. Therefore, these compounds have no important chemical structure in common. Such being the case, the inventions as set forth in the above claims are not considered as relating to a single invention or a group of inventions so linked as to form a single general inventive concept.

In the description, only a part of the compounds having specific choices are cited among the compounds corresponding to the structural formula described in the claims.

Further, it is obvious that there are a number of documents denying the novelty and inventive step of the inventions as set forth in these claims. Therefore, it is impossible in practice to search documents of the prior arts all over the scope.

Thus, claims 1 to 32 and 34 fail to satisfy the specified requirements to such an extent as any enabling meaningful international search report.

In this international search report, documents of prior art have been examined based on the compounds particularly cited in the description.